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Unique zinc-induced α-elimination-rearrangement of longibornyl bromide: Generation of isolongifolene/1, 1-dimethyl-7-isopropyltetralin†

U R Nayak*, V S Dalavoy & V B Deodhar
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Received 17 February 1989; accepted 6 March 1989

When longibornyl bromide(**1**) is refluxed with zinc dust in dioxane or in acetic acid, it gives an abnormal olefin, isolongifolene(**2**). While refluxing **1** with zinc in benzene yields a mixture of **2** and its further rearranged product **3**, in toluene only **3** is obtained. The normal saturated hydrocarbon, longibornane (**4**), is generated only when **1** is refluxed with zinc in ethanol; however, the olefin **5** (36%) is also formed. These anomalous results have been rationalized by invoking a carbene intermediate **7** and formation of the cyclopropane intermediate **8** as the precursor for the isolated products **2, 3** and **5**.

While investigating[1] the zinc-induced Grob-fragmentation of some longi-bornane-based 1,4-dihalides, it became necessary to study the action of zinc on a related monobromide, viz. longibornyl bromide (**1**) also. The formation of the thoroughly abnormal products isolongifolene (**2**)/1, 1-dimethyl-7-isopropyltetralin (**3**) on refluxing **1** with zinc in polar/non-polar solvents and characterization of these are described in this paper.

Replacement of halogen by hydrogen in haloalkanes using zinc in organic solvents is well-documented[2]. However, when **1** was refluxed for 2 hr with zinc dust in dioxane, there was no evidence of any longibornane[3] (**4**) in the product. The resulting single olefin was shown to have a rearranged skeleton of the type isolongifolene[4] (**2**). On changing the solvent to refluxing benzene, a mixture of **2** and the tetralin[5] **3** was formed while refluxing in toluene gave a liquid in which **2** was absent and consisted only of its further rearranged product **3** (actually the disproportionated mixture of **3** and the mono-olefins derived from the bicyclic diene[5] intermediate). The mixture obtained on refluxing **1** with zinc dust in ethanol was, however, quite different and was resolved (silver nitrate-impregnated silica gel) into the saturated longibornane (**4**) and an olefin identified readily as longifolene (**5**). Refluxing **1** with zinc dust in acetic acid essentially gave isolongifolene (**2**).

The above unusual results can be rationalized mechanistically by invoking a carbene intermediate **7** which is generated from the initially formed longibornyl zinc bromide (**6**) via a four-membered cyclic transition state **6a** (cf Scheme 1) involving an α-proton elimination in **1** leading to longicyclene[6] (**8**) as the primary product. Conceivably, on exposure to the acidic zinc bromide which is also formed in the reaction (Scheme 1), a facile cleavage of the cyclopropane moiety in **8** followed by rearrangement generates **5** and the further rearranged products **2** and/or the tetralin **3** depending upon the stringency of the reaction conditions. Although longicyclene (**8**) has not been actually isolated in any of the above reactions, there is no doubt that it is the precursor for the observed products. While cyclopropane formation in the case of branched-chain alkyl halides by α-proton elimination[7] with base is known, such a mechanism for the reaction of zinc with an alkyl bromide of the type **1** is now proposed for the first time. Finally, it is also noteworthy that the normal saturated hydrocarbon **4** (39% yield) is only formed when the bromide **1** is refluxed with zinc in ethanol, although the abnormal olefin **5** (longifolene[8], 36%) is also generated in the reaction; the role played by the alcoholic solvent in the product development, however, remains obscure.

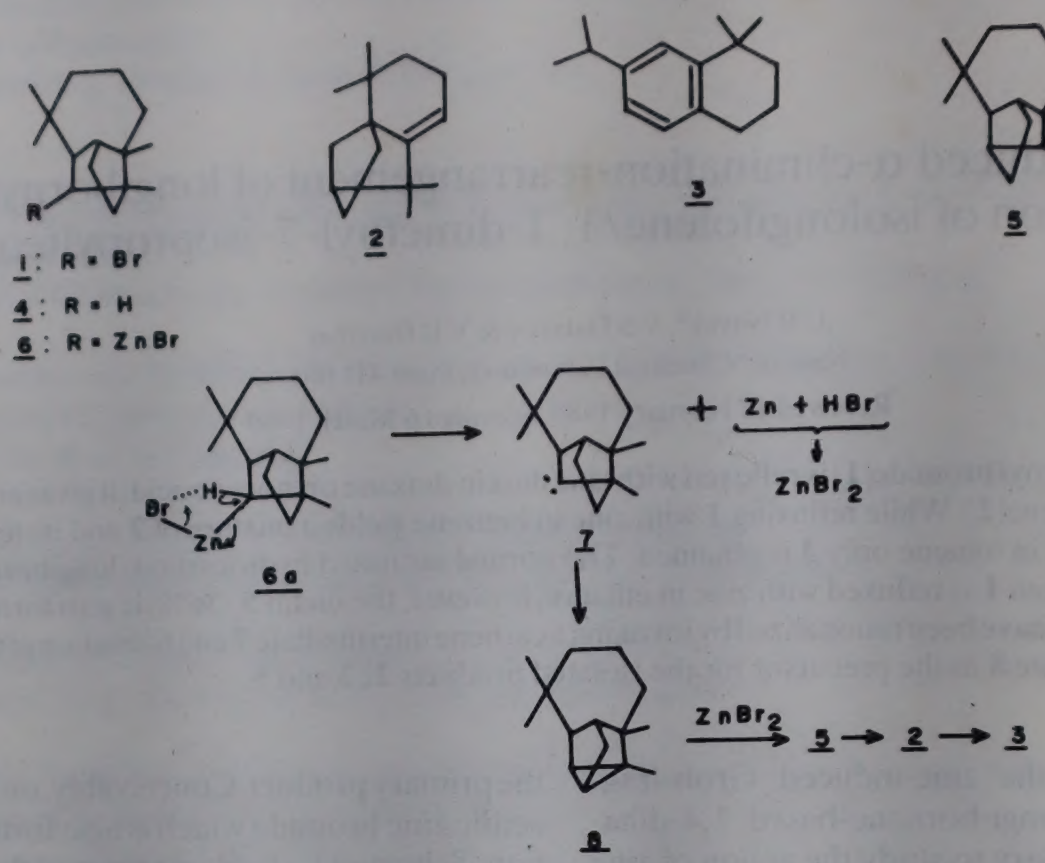
Experimental Procedure

Light petroleum refers to fraction b.p. 60-80°. Solvent extracts were dried over anhydrous Na_2SO_4. Zinc dust used was from a freshly opened bottle. 30% HBr in AcOH solution used was the product of Eastman Organic Chemicals (USA).

Longibornyl bromide (**1**)

This known[9] compound was prepared by a more convenient method. Longifolene (60g) in benzene (600 ml) was cooled in ice-water, treated with 30% HBr in AcOH solution (100 ml) and kept at room temperature for 4 days. Water (200 ml) was added, the benzene layer was separated, successively washed with $NaHCO_3$ aq, water, brine and dried. Removal of

†NCL Communication No. 4648.



SCHEME I

solvent and recrystallization of the residue gave **1** as colourless crystals, m.p. 69-70° (79 g).

Action of zinc dust on **1** *in dioxane: Formation of isolongifolene* (**2**)

A mixture of **1** (2.85g), zinc dust (0.72 g) and dioxane (50 ml) was refluxed for 2 hr, cooled and filtered. The filtrate was diluted with water (100 ml), extracted with light petroleum, washed with brine, dried, solvent removed and the residue distilled to give **2** as a colourless liquid, b.p. 95°/1mm (1.77 g, 87%). **2** was fully characterised by its IR and PMR

Action of zinc dust on **1** *in AcOH: isolongifolene* (**2**)

A mixture of **1** (2.85g), zinc dust (2g) and AcOH (50 ml) was refluxed for 2 hr, worked up as above and the residue distilled to yield a liqid (1.84g, 90%) characterized as **2** (IR/PMR).

Action of zinc dust on **1** *in benzene: isolongifolene* (**2**) *and-tetralin* (**3**)

A mixture of **1** (2.85g), zinc dust (0.72g) and benzene (50 ml) was refluxed for 2 hr, cooled and filtered. Removal of solvent from the filtrate and distillation of the residue gave a liquid, b.p. 120° (bath)/1mm (1.2g); PMR spectrum indicated it to be a mixture of **2** and **3** plus monoolefins[5].

Action of zinc dust on **1** *in toluene: Tetralin* **3**

A mixture of **1** (2.85g), zinc dust (0.72g) and toluene (50 ml) was refluxed for 2 hr, cooled and filtered. Removal of solvent from the filtrate and distillation of the residue gave a liquid bp. 120° (bath)/1mm (1.25 g, 61%); its PMR spectrum indicated it to be the disproportionated mixture[5] of **3** and mono-olefins.

Action of zinc dust on **1** *in ethanol: longibornane* (**4**) *and longifolene* (**5**)

A mixture of **1** (2.85 g), zinc dust (2 g) and EtOH (50 ml) was refluxed for 6 hr, cooled and filtered. The filtrate was diluted with water, extracted with light petroleum, washed with brine, dried, solvent removed and the mixture (PMR) was chromatographed over 15% $AgNO_3$ – silica gel[10] (60 g; 48 cm × 1.5 cm). Fr 1, light petroleum, 2 × 25 ml, pure **4**[3] (IR, PMR; 0.81g, 39%). Fr 2, benzene, 2 × 25 ml, pure **5** (IR/PMR; 0.74 g, 36%).

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A stereoselective synthesis of 12-hydroxy-(*E*)-γ-bisabolene

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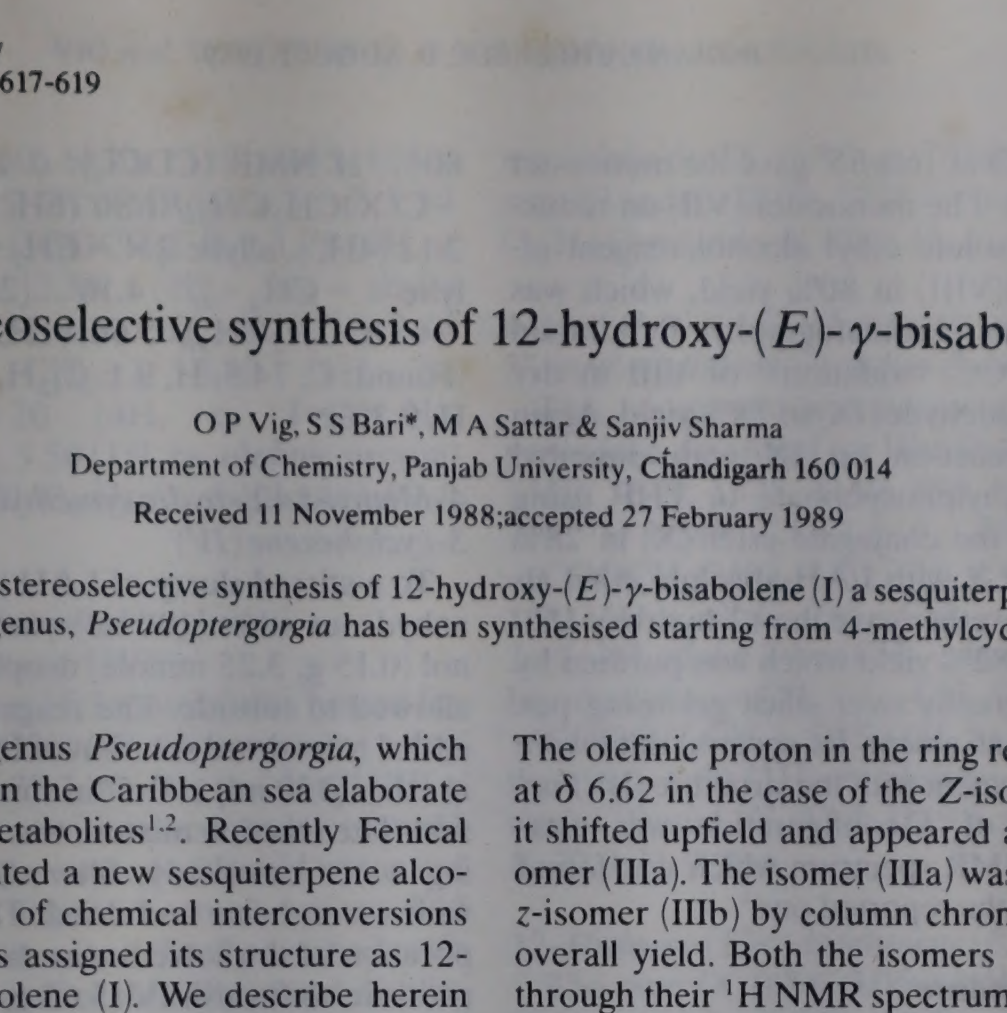
Received 11 November 1988;accepted 27 February 1989

A convenient stereoselective synthesis of 12-hydroxy-(*E*)-γ-bisabolene (I) a sesquiterpene alcohol isolated from the genus, *Pseudoptergorgia* has been synthesised starting from 4-methylcyclohex-3-enone (II)

The species of the genus *Pseudoptergorgia*, which occur in abundance in the Caribbean sea elaborate several terpenoid metabolites[1,2]. Recently Fenical and coworkers[3] isolated a new sesquiterpene alcohol and on the basis of chemical interconversions and spectral analyses assigned its structure as 12-hydroxy-(*E*)-γ-bisabolene (I). We describe herein an unambiguous and convenient synthesis of I.

Our approach to I is outlined in Scheme 1. The starting, 4-methylcyclohex-3-enone (II)[4] was subjected to modified Wittig reaction[5] using dimethyl 1-ethoxycarbonylethylphosphonate, in DME and NaH as the base. A 1 : 1 mixture (PMR) of α,β-unsaturated esters (IIIa) and (IIIb) was obtained. The olefinic proton in the ring resonated downfield at δ 6.62 in the case of the *Z*-isomer (IIIb) whereas it shifted upfield and appeared at δ 5.66 in (*E*)-isomer (IIIa). The isomer (IIIa) was separated from its *z*-isomer (IIIb) by column chromatography in 32% overall yield. Both the isomers were characterized through their ^{1}H NMR spectrum.

Reduction of IIIa with LAH-absolute ethyl alcohol in ether[6] furnished the allylic alcohol(IV) in 82% yield. The allylic alcohol(IV) was converted into its mesylate(V)[7] as usual at 10°, which was reacted further as such with ethyl monosodiomalonate in benzene-DME[8] to furnish the diester (VI) in 59% yield. The diester (VI) when heated with a mixture of mo-



Scheme 1

ist NaCl and DMSO at 160-65° gave the monoester (VII)[9] in 84% yield. The monoester (VII) on reduction with LAH/absolute ethyl alcohol reagent afforded the alcohol(VIII) in 80% yield, which was purified by column chromatography. Pyridinium chlorochromate (PCC) oxidation[10] of VIII in dry CH_2Cl_2 led to the aldehyde (IX) in 78% yield. Again modified Wittig reaction on IX with dimethyl 1-ethoxycarbonylethylphosphonate in THF using NaH as base gave the conjugate ester (X) in 78% yield. Reduction of X with LAH-absolute ethyl alcohol reagent in dry ether gave the 12-hydroxy-(*E*)-γ-bisabolene (I) in 82% yield which was purified by column chromatography over silica gel using pet. ether-ethyl acetate as eluent. Its spectral data were found in good agreement with the structure (I)[3]. Further confirmation of *E*-configuration was established from ^{13}C NMR spectrum which was found to be identical with the reported one[3].

Experimental Procedure

B.ps are uncorrected. IR spectral (ν_{max} in cm^{-1}) were recorded as thin films on a Perkin Elmer infracord 337 spectrophotometer with NaCl optics, ^1H NMR spectra were taken at 90 MHz in CCl_4 or $CDCl_3$ using TMS as an internal standard on a Varian EM-390 spectrometer, mass spectra on VG micromass 7070F spectrometer and UV spectra on Hitachi model 330 spectrophotometer. Neutral alumina of Brockman activity (BDH) and silica gel (100-200 mesh, Acme) was used for column chromatography. All solvents and reagents were purified and dried by standard techniques.

4-*Methyl*-1-(1′-*carbethoxy*)*ethylidene*-3-*cyclohexene* (*IIIa*)

A 50% mineral oil suspension of NaH (5.28 g, 110 mmole) washed with dry *n*-hexane was placed in DME (110 ml) and dimethyl 1-ethoxycarbonylethylphosphonate (25.20 g, 120 mmole) was added dropwise below 20° with continuous stirring until the gas evolution ceased. To the resulting yellow solution was added the ketone II (11 g, 100 mmole) slowly below 10°. After the addition, stirring was continued for 4 hr. The reaction mixture was heated at 60° for 1 hr, decomposed with ice old water and extracted with ether. The ethereal extract was successively washed with water, brine and dried. Removal of the solvent and distillation under reduced pressure afforded (13.5 g, 70%) a mixture of IIIa and IIIb in the ratio (1 : 1), b.p. 115-17°/5 mm. Compound IIIa was purified by repetitive column chromatography over silica gel using pet. ether-ethyl acetate as eluent; yield 6.2 g (32%); IR (neat): 2900, 1720, 1450, 1380, 1240, 1120, 1035, 860, 830 and 805. ^1H NMR ($CDCl_3$): δ 1.30 (3H, t, J = 6 Hz, $-COOCH_2CH_3$), 1.80 (6H, s, allylic $2\times -CH_3$), 2.12 (4H, s, allylic $2\times -CH_2-$), 3.20 (2H, bs, diallylic $-CH_2-$), 4.16 (2H, q, J = 6 Hz, $-COOCH_2CH_3$), 5.66 (1H, bs, olefinic proton) (Found: C, 74.5; H, 9.1. $C_{12}H_{18}O_2$ requires C, 74.2; H, 9.3%).

4-*Methyl*-1-(2′-*hydroxymethyl*)*ethylidene*-3-*cyclohexene* (*IV*)

To a stirred slurry of LAH (1.90 g, 50 mmole) in anhydrous ether (100 ml) was added absolute ethanol (0.15 g; 3.25 mmole) dropwise and the reaction allowed to subside. The reagent thus obtained was added to a stirred solution of IIIa (8.73 g, 45 mmole) in ether (150 ml) at 0-5° in small portions during 30 min. The reaction mixture was decomposed by adding water cautiously, filtered, the filtrate washed with water, brine and dried. The residue after evaporation of the solvent was distilled under reduced pressure to furnish IV (5.65 g, 82%); b.p. 97-98°/5 mm; IR (neat): 3340, 2900, 1420, 1350, 1300, 1235, 1050, 1020 and 815; ^1H NMR ($CDCl_3$): δ 1.80 (6H, s, allylic $2\times CH_3$), 2.25 (4H, bs, allylic $2\times -CH_2-$), 3.00 (2H, bs, diallylic, $-CH_2-$), 4.1 (2H, s, $-CH_2OH$), 5.45 (1H, bs, olefinic proton) (Found: C, 78.7; H, 10.0. $C_{10}H_{16}O$ requires C, 79.0; H, 10.5%).

4-*Methyl*-1-(1′-*methanesulphonyloxymethyl*)-3-*cyclohexene* (*V*)

To a stirred solution of IV (7.6 g, 50 mmole) in anhydrous CH_2Cl_2 (50 ml), maintained at 0 to 10°, was added methenesulphonyl chloride (7.5 g, 65.5 mmole) in CH_2Cl_2 (20 ml). After the addition was over, stirring was continued for 30 min more. The reaction mixture was washed successively with dilute HCl (10%), saturated aq $NaHCO_3$ water and brine. The methylene chloride extract was dried ($CaCl_2$). Evaporation of the solvent gave the mesylate V (9.9 g, 86%). The crude mesylate was used as such for the next operation.

4-Methyl-1-[1′-(2″,2″-*diethoxycarbonyl*)*ethyl*] *ethylidene*-3-*cyclohexene* (*VI*)

The mesylate V (7.66 g, 33.3 mmole) was added to ethyl monosodiomalonate [from sodium (0.85 g, 36.9 mmole) and ethyl malonate (5.4 g, 33.8 mmole)] in dry benzene (100 ml) in the presence of DMF (10 ml). The reaction mixture was refluxed for 16 hr, washed with water and the water extract was back extracted with ether (50 ml). The combined organic extract was washed with water and dried. Evaporation of the solvent and fractional distillation at 139-40°/5-6 mm afforded VI (5.78 g, 59%); IR

(neat): 2910, 1730-1750, 1430, 1350, 1085, 1040, 855, 820, 790 and 715; ^{1}H NMR ($CDCl_3$): δ 1.30 (6H, t, J = 6 Hz, 2 × $-COOCH_2CH_3$), 1.70 (6H, s, allylic 2 × $-CH_3$), 2.30 (4H, bs, allylic 2 × $-CH_2-$), 2.55 (2H, d, $-CH_2-CH<$), 2.85 (2H, bs, diallylic CH_2-), 3.40 (1H, bt, $-CH_2-CH<$), 4.20 (4H, q, J = 6 Hz, 2 × $-COOCH_2CH_3$), 5.50 (1H, bs, olefinic proton) (Found: C, 68.9; H, 9.0. $C_{17}H_{26}O_4$ requires C, 69.4; H, 8.8%).

4-*Methyl*-1-[1′-(2″-*ethoxycarbonyl*)*ethyl ethylidene*]-*cyclohex*-3-*ene* (*VII*)

The diester VI (4.5 g, 15.3 mmole) was heated for 8 hr at 160-65° in DMSO (40 ml) containing a few drops of water (0.6 g, 33.3 mmole) and NaCl (0.9 g, 15.4 mmole). DMSO was removed under reduced pressure and the residue treated with cold water and extracted with ether. Ethereal extract was washed with water several times and finally washed with brine and dried. Removal of the solvent and distillation of residue under diminished pressure yielded VII (2.86 g, 84%), b.p. 107-8°/3 mm; IR (neat): 2900, 1735, 1345, 1330, 1150, 1110, 1090, 1035, 830, 815, 785 and 735; ^{1}H NMR ($CDCl_3$): δ 1.25 (3H, t, J = 6 Hz, $-COOCH_2CH_3$), 1.67 (6H, s, allylic 2 × CH_3), 2.20-2.45 (8H, m, allylic 3 × $-CH_2-$ and $-CH_2-\overset{O}{\overset{\|}{C}}-$), 2.85 (2H, bs, diallylic $-CH_2-$), 4.15 (2H, q, J = 7 Hz, $-COOCH_2CH_3$), 5.40 (1H, bs, olefinic proton) (Found: C, 75.2; H, 9.7. $C_{12}H_{22}O_2$ requires C, 75.7; H, 9.9%).

4-*Methyl*-1-[1′-(3″-*hydroxypropyl*) *ethylidene*]-*cyclohex*-3-*ene* (*VIII*)

This compound was prepared according to the procedure described for IV.

4-*Methyl*-1-[1′-(3″-*oxopropyl*)*ethylidene*]-*cyclohex*-3-*ene* (*IX*)

To a suspension of pyridinium chlorochromate (2.20 g, 10.18 mmole) in anhydrous CH_2Cl_2 (30 ml) was added VIII (1.20 g, 6.67 mmole) in CH_2Cl_2 (20 ml) in one portion with stirring at 10°. Stirring was continued for 4 hr more, ether (50 ml) was added to it and the supernatant liquid decanted from the black gum. The insoluble residue was washed thoroughly with anhydrous ether (3 × 50 ml), when a black granular solid was obtained. The combined organic extract was passed through a short column of neutral alumina and dried. Removal of the solvent under reduced pressure gave the sharp smelling aldehyde IX (0.93 g, 78%), b.p. 108-10°/5-6 mm; IR (neat): 2690, 1725 (Found; C, 80.7; H, 9.9. $C_{12}H_{18}O$ requires C, 80.9; H, 10.1%).

4-*Methyl*-1-[1′-(4″-*ethoxycarbonyl-pent*-3″-*enyl*)*ethylidene*]-*cyclohex*-3-*ene* (*X*)

This compound was prepared according to the procedure described for IIIa; IR (neat): 2900, 1715, 1450, 1340, 1325, 1140, 840, 825, 785, 740 and 715; ^{1}H NMR ($CDCl_3$): δ 1.25 (3H, t, J = 6 Hz, $-COOCH_2CH_3$), 1.70 (9H, s, allylic 3 × $-CH_3$), 1.90 (4H, s, allylic 2 × $-CH_2-$ in the side chain), 2.15 (4H, allylic 2 × $-CH_2-$ in the ring), 2.80 (2H, bs, diallylic $-CH_2-$), 4.15 (2H, q, J = 6 Hz, $-COOCH_2CH_3$), 5.45 (1H, bs, olefinic proton in the ring), 6.60 (1H, m, olefinic proton in the side chain) (Found: C, 77.4; H, 9.6. $C_{17}H_{26}O_2$ requires C, 77.9; H, 9.9%).

12-*Hydroxy*-(*E*)-γ-*bisabolene* (*I*)

The ester (X, 0.8 g, 3.05 mmole) was reduced to I (0.55 g, 82%) according to the procedure described for IV; MS: m/z 219.20 (M^+); UV (MeOH): 252 nm (ε, 4950); IR (neat): 3380 (−OH), 2910, 1665, 1450, 1370, 1340, 840, 830, 790,740 and 715; ^{1}H NMR ($CDCl_3$): δ 1.70 (9H, allylic 3 × $-CH_3$), 2.00-2.30 (8H, m, allylic 4 × $-CH_2-$), 2.80 (2H, bs, diallylic CH_2-), 4.00 (2H, bs, $-CH_2OH$), 5.33-5.45 (2H, m, two olefinic protons, one in the ring and one in the side chain) (Found: C, 81.5; H, 10.0. Calc. for $C_{15}H_{25}O$: C, 81.8; H, 10.9%); ^{13}C NMR chemical shifts for C-7, C-11 and C-14 were at δ 29.8, 27.3 and 18.4 respectively, confirming the *E*-configuration.

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Studies on substituted-9-azabicyclo[3.3.1]nonan-3-ones†

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Some 9-γ-thio(4-substituted phenyl)propyl-9-azabicyclo[3.3.1] nonan-3-ones (**9-14**), and 9-γ-[(4-fluorobenzoyl)propyl]-9-azabicyclo[3.3.1]nonan-3-one (**7**) have been synthesized by the condensation of 9-azabicyclo[3.3.1]nonan-3-one with γ-chloropropylarylsulphides and γ-chloro-4-fluorobutyrophenone, respectively. Compound **7** was reduced to give the alcohol **8**. In order to synthesize 9-azabicyclo[3.3.1]nonan-3, 7-dione, different routes have been attempted. Ultimately, its 2,6-diethoxycarbonyl derivative (**28**) was synthesized from 1,3-diethyl 2-aminoglutaconate via Michael addition of 1,3-diethylglutaconate followed by Dieckman cyclization. Some of the compounds showed hypotensive and antiinflammatory activities.

Certain substituted 9-azabicyclo[3.3.1]nonanes have been found to possess a wide spectrum of biological activities such as anticholinergic[1,2], antidepressant[3], neuroleptic[4-6], cardiovascular[7,8], antiparkinsonian[9,10], antidiabetic[11,12] and antitussive[13] activities. As these compounds incorporate active pharmacophores in the 9-azabicyclo[3.3.1]nonan systems, it appeared of interest to synthesize compounds having the thioarylpropyl and 4-fluorobenzoylpropyl groups[14,15] (active pharmacophores for CNS/CVS activity) fused to 9-azabicyclo[3.3.1]nonanes. The present paper describes the synthesis, biological activity and molecular conformation of these compounds.

Chemistry and molecular conformation

The required 9-azabicyclo[3.3.1]nonan-3-one (**4**) was synthesized either directly by the Robinson-Schopf condensation of 1,3-acetonedicarboxylic acid (**1**), glutaraldehyde (**2**) and ammonium chloride, or alternatively by the Pd/C reduction of the 9-benzyl derivative obtained by the condensation of **1, 2** and benzylamine[16]. The Grignard reaction of **3** with phenyllithium and bromobenzene in dry ether, followed by catalytic (Pd/C) debenzylation in ethanol gave 3-phenyl-9-azabicyclo[3.3.1]nonan-3-ol (**6**) (Scheme 1).

Condensation of **4** with γ-chloro-4-fluorobutyrophenone and 3-chloropropyl(4-substituted phenyl)sulphide[14] in the presence of baked Na_2CO_3, NaI and dry DMF gave the corresponding 9-γ-[4-fluorobenzoyl)propyl]-9-azabicyclo[3.3.1]nonan-3-one (**7**) and 9-γ-thio(4-substituted phenyl)propyl-9-azabicyclo[3.3.1]nonan-4-ones (**9-14**) (Table 1) The compound **7** was reduced with $NaBH_4$ in dry methanol to give the alcohol **8**.

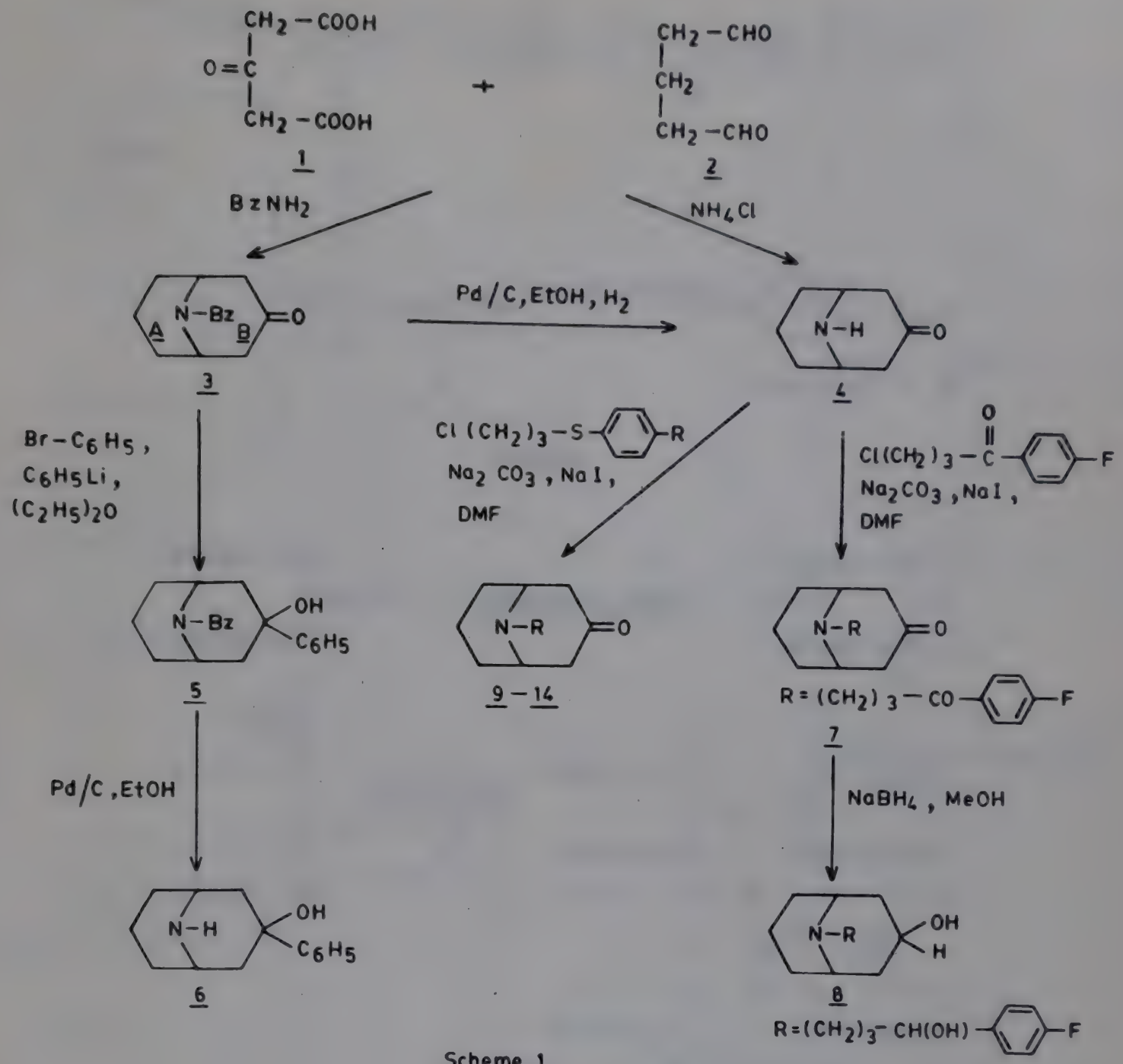
The conformations of rings A and B in the 9-substituted-9-azabicyclo[3.3.1]nonan-3-ones have been assigned on the basis of their PMR spectra. In the PMR spectrum of **3** the H-1 and H-5 appeared as a poorly resolved pseudo-triplet at δ3.25 with a band width of ≈ 19 Hz, axial H-2 and H-4 appeared as a double doublet centred at δ2.7 with separations: J H-2 (H-4) axial—H-2 (H-4) equatorial ≈ 16.5 Hz, and J H-1(H-5)—H-2(H-4) axial ≈ 6.5 Hz. The doublet at δ2.2 (J ≈ 16 Hz) may be assigned to H-2, H-4 equatorial protons [J H-2(H-4) equatorial —H-2(H-4) axial ≈ 16.5 Hz], while the unresolvable fine structures may be due to long range couplings, J H-1(H-5)—H-2(H-4) equatorial ≈ 1.5 Hz. These results were in agreement with the earlier observed results[17], thus suggesting it to have a double chair conformation. Similar pattern in the PMR spectra of the other compounds (**7, 9-14**) confirmed the double chair conformation in these compounds.

Table 1—Characterization data of compounds **9-14**

Compd	*R*	Mol formula	m.p.[a] (°C)	Yield (%)
9	H	$C_{17}H_{23}NOS.HCl$	152	80.9
10	Cl	$C_{17}H_{22}Cl\,NOS.\,HCl$	204	86.8
11	NO_2	$C_{17}H_{22}N_2O_3S.HCl$	101-2	60.1
12	NHAc	$C_{19}H_{26}NO_2S.\,HCl$	208	59
13	OCH_3	$C_{18}H_{25}NO_2.S.\,HCl$	190	59.5
14	CH_3	$C_{18}H_{25}NOS.\,HCl$	198	57.2

(a) Crystallized from ethanol.

† CDRI Communication No. 4367

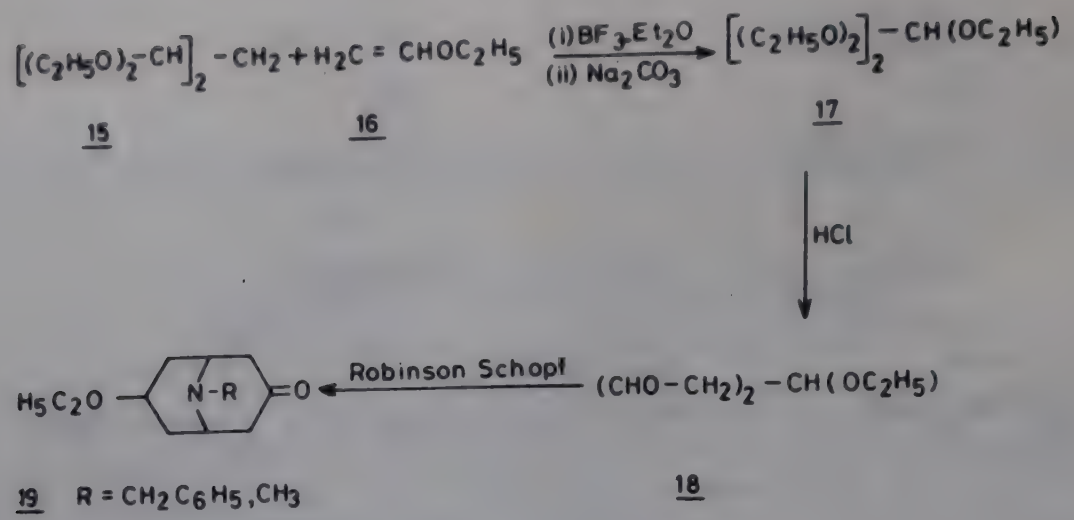


Scheme 1

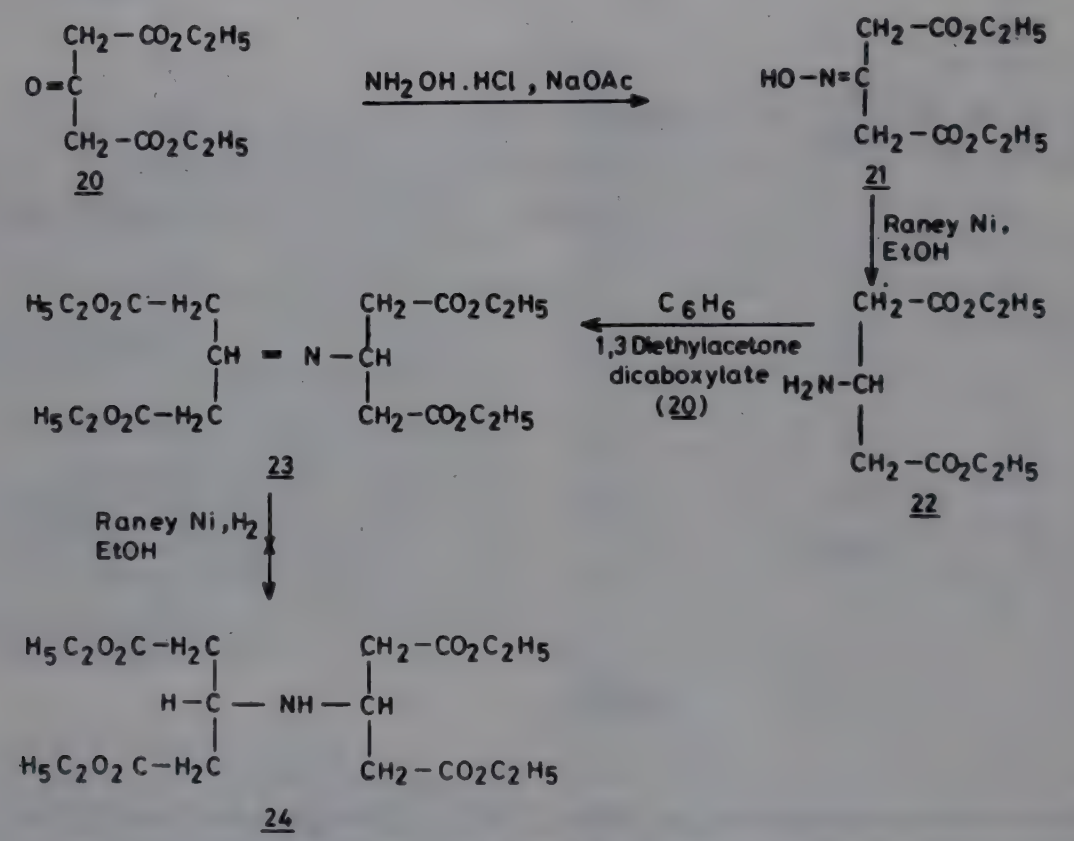
The double chair conformation of these compounds was also supported by the fact that the $NaBH_4$ reduction of 9-γ-(4-fluorobenzoyl)propyl-9-azabicyclo[3.3.1]nonan-3-one (**7**) gave exclusively the 3α-derivative (**8**) in which the OH group was axially disposed. In its PMR the H-3 appeared as a symmetric quintet centred at δ4.12 with spacings of ≈ 7.0 Hz, while the H-1 and H-5 appeared as poorly resolved signals at δ3.0 with a band width of ≈ 25 Hz. The H-2, H-4 axial protons appeared at δ2.5 and 2.73 as a double doublet, while the H-2, H-4 equatorial protons appeared at δ2.2 and 2.38 respectively, with a band width of ≈ 9 Hz. This pattern of proton signals can be explained if the rings in **7** are in a double chair conformation, whereby the approach of the reducing agent to **7** takes place from the exo face. Thus the OH group in **8** would take up axial orientation because the endo approach of reducing agents is hindered in **7**.

The synthesis of 7-substituted-9-azabicyclo[3.3.1]nonan-3-one was first attempted according to reported method[18] (Scheme 2) by the condensation of β-ethoxyglutaraldehyde[19], 1,3-acetonedicarboxylic acid and benzyl/methyl amine, under Robinson-Schopf conditions when 7-ethoxy-9-benzyl/methyl-9-azabicyclo[3.3.1]nonan-3-one (**19**, R = $CH_2C_6H_5$/CH_3) were obtained in 20 and 14% yields, respectively. As the yields of β-ethoxyglutaraldehyde (**18**) synthesized according to reported method[19], from malonicdialdehydetetraethyl acetal (**15**) and ethyl vinyl ether (**16**) was also low, some alternative routes were attempted to improve the yields.

In the first approach (Scheme 3) diethyl 1,3-acetonedicarboxylate (**20**)[20], was converted into its oxime (**21**), which on reduction over Raney nickel in ethanol gave 1,3-diethyl-2-amino-glutarate (**22**). Compound **22** was condensed with **20** to give 1,3-diethyl-3-[3-diethylglutaryl]-imminoglutarate (**23**). Attempts to hydrogenate the double bond in **23** with



Scheme 2

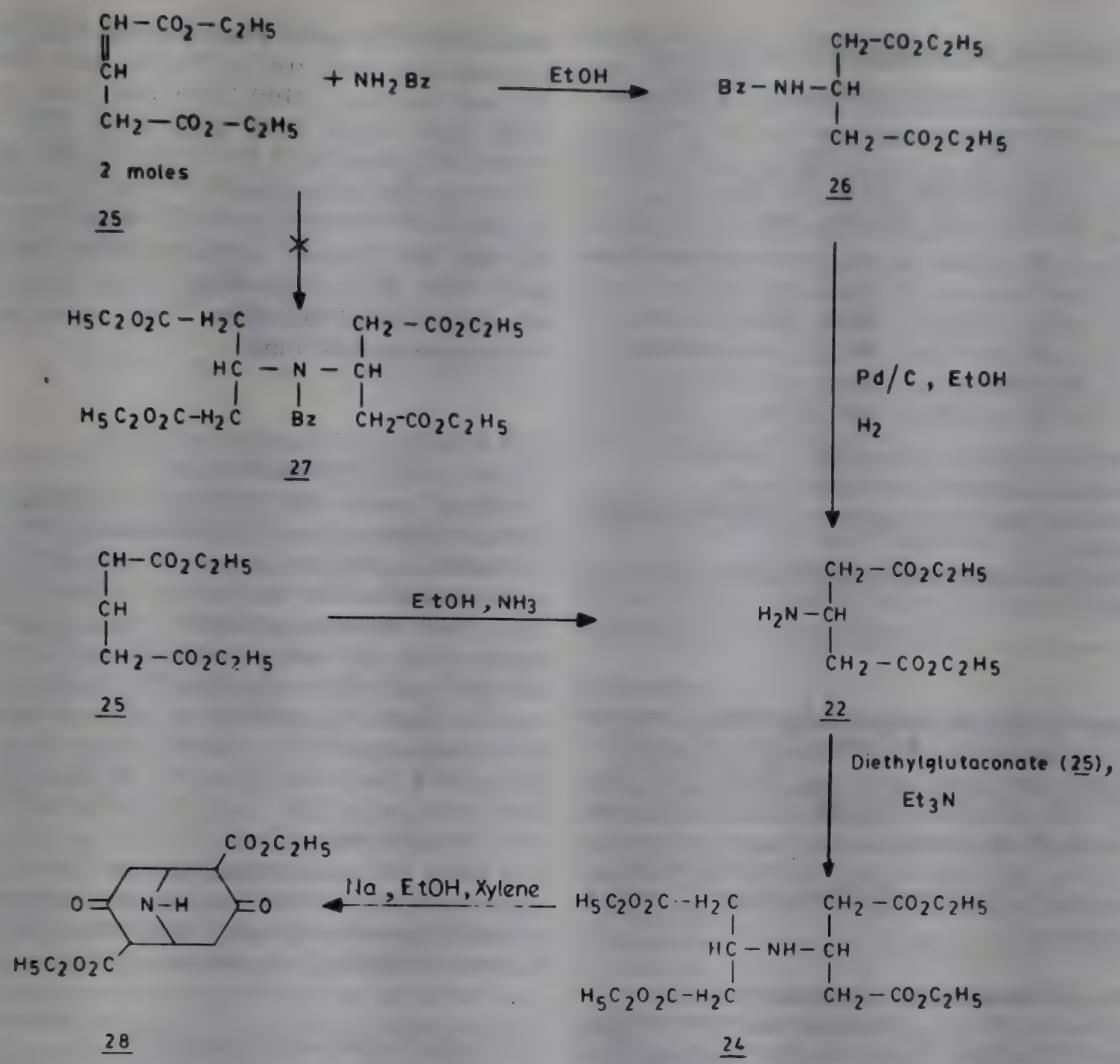


Scheme 3

Pd/C or Raney nickel in ethanol were unsuccessful, So, an alternative route was attempted (Scheme 4) in which two moles of diethylglutaconate (**25**) and one mole of benzylamine were condensed under Michael conditions when 1,3-diethyl 2-benzylamino-glutarate (**26**) instead of the required N,N-bis-(1,3-diethylglutaryl)benzylamine (**27**) was obtained. In order to get the required **27**, compound **26** was again treated with one mole of ethyl 1,3-diethylglutaconate (**25**) under forced Michael conditions such as higher temperatures and in the presence of base triethylamine, but the required **27** was not obtained probably due to steric hindrance. Compound **26** was debenzylated over Pd/C in ethanol in a Parr apparatus to give 1,3-diethyl-2-aminoglutarate (**22**), which was also obtained in one step from **25** by literature method[21], by passing dry ammonia through an ethanolic solution of **25** for 36 hr. Compound **22** underwent Michael condensation with **25** in the presence of triethylamine, to give N,N-bis(1,3-diethylglutaryl)amine (**24**). Compound **24** was cyclized in the presence of sodium sand, dry xylene and absolute ethanol to give diethyl 9-azabicyclo[3.3.1]nonan-3, 7-dione-2,6-carboxylate (**28**), which was characterised on the basis of its PMR and mass spectrum (Scheme 4).

Pharmacological activity

Compounds **5-14** were tested for their diuretic activity (furosemide as standard), at 30 mg/kg dose, prevention of passive cutaneous anaphylaxis (PCA) and



Scheme 4

antiinflammatory activity against carrageenin induced oedema in male mice at 60 mg/kg dose, and 10 mg/kg i.p. for CNS and other activities like antiacetylcholine, antiadrenaline, antihistamine, analgesic, antireserpine and anti-isoprenaline activities. These compounds were tested for their effect on blood pressure and respiration in anaesthetized cats by administering different doses. The significant results are summarized in Table 2. Among these compound **7** showed good hypotensive activity, while **10** and **13** had antiinflammatory activity.

Experimental Procedure

All compounds were routinely checked for their structures by IR spectra on a Perkin-Elmer 157 infrared spectrophotometer (ν_{max} in cm^{-1}), PMR recorded on Perkin-Elmer R-32 (90 MHz) and EL-360 (60 MHz) spectrophotometers (chemical shift in δ(scale) using TMS as an internal reference, and mass spectra on a Jeol JMS D-300 instrument. Melting points were taken in an electrically heated apparatus and are uncorrected. All the compounds were analysed for carbon, hydrogen, nitrogen and the results are within ± 0.4% of the calculated value.

3-*Phenyl*-9-*benzyl*-9-*azabicyclo*[3.3.1]*nonan*-3-*ol*(**5**).

Dry bromobenzene (1.72 g, 10.09 mmole) was added dropwise to a stirred suspension of lithium wire (0.15 g, 21.4 mmole) in dry ether (10 ml). The reaction mixture was refluxed till all the lithium dissolved (1 hr). The compound **3** (2.29 g, 10.0 mmole) was added slowly to the reaction mixture at − 5°, and then refluxed for 5 hr. It was cooled to 0° and water (2.0 ml) was added. The separated ether layer was dried (Na_2SO_4), concentrated and purified by passing

Table 2—Pharmacological activities of compounds

Compd	CVS activity[a] in mg/kg i.v.				Other activities[b] and toxicity
	1 mg		5 mg		
	Fall in B.P.(mm)	Duration (min)	Fall in B.P.(mm)	Duration (min)	
5	16	Tr	36	11	Diuretic[d] 18(30)
7	40	14	72	110	
9	24	10	20	Tr	
10	18	Tr	50	4	AI[c] 18(30)
13	No effect		28	3	AI 17(30
14	12	Tr	20	Tr	

(a) Fall in blood pressure in mm of Hg; Tr = Transient.

(b) Figures in parentheses indicate dose in mg/kg.

(c) Antiinflammatory activity against carrageenin induced oedema in mice.

(d) Diuretic activity (oral); figure in parenthesis describes dose in mg/kg.

through a fluorisil column using $CHCl_3$—MeOH (2%) as eluant to give **5** in 39% yield (1.2 g) m.p. 98°; IR(KBr): 3300, 2900, 1620, 1460, 1300, 1200, 1160, 1120, 1080, 1040, 960, 920, 900, 860, 820, 800, 760, 740, 720; PMR ($CDCl_3$): 1.0-3.2 (m, 12H, aliphatic H), 3.8 (s, 2H, $CH_2-C_6H_5$), 5.2 (d, 1H, OH, exchangeable with D_2O), 6.8-9.7 (m, 10H, Ar-H): MS: m/z 308 (M^+).

3-*Phenyl*-9-*azabicyclo*[3.3.1]*nonan*-3-*ol* (**6**)

A mixture of **5** (0.4 g, 1.3 mmole) and Pd/C (0.2 g) in ethanol (10 ml) was shaken in a Parr apparatus with hydrogen at 50 psi for 8 hr at 32°. The reaction mixture was filtered, concentrated and the residue crystallized from ethanol to give **6**, yield 0.2 g (70.7%), m.p. 246°; IR (KBr): 3400, 3000-3850, 1620, 1510, 1440, 1400, 1340, 1300, 1200, 1160, 1130, 1100, 1040, 970, 940, 860, 820, 780, 770, 720, PMR ($CDCl_3$ + DMSO d_6): 1.0-1.7 (m, 6H, H-6, H-7, H-8), 2.2 (d, 2H, H-2, H-4 equatorial), 2.5 (dd, 2H, H-2, H-4 axial), 3.2 (bs, 2H, H-1, H-5), 5.3 (d 1H, OH, exchangeable with D_2O), 7.25 (bs, 5H, Ar-H), 7.8 (bs, 1H, NH, exchangeable with D_2O); MS: m/z 217 (M^+).

9-γ-(4-*Fluorobenzoyl*)*propyl*-9-*azabicyclo*[3.3.1]*nonan*-3-*one* (**7**)

A mixture of **4** (0.695 g, 5 mmole), γ-chloro-4-fluorobutyrophenone (1.01 g, 5.04 mmole), baked Na_2CO_3 (0.265 g, 2.5 mmole), NaI (0.0375 g, 0.25 mmole) and dry DMF (10 ml), was stirred at 70° for 24 hr. The reaction mixture was cooled and water (25 ml) was added. The separated oil was extracted with chloroform (2 × 20 ml), dried (Na_2SO_4) and concentrated to give **7** as an oil, which was converted into its hydrochloride, yield 0.62 g (36.5%), m.p. 140-41°; IR(Neat) (free base): 3400, 2900, 1680, 1600, 1500, 1420, 1380, 1220, 1160, 1050, 1000, 820, 760; PMR($CDCl_3$, free base): 3.1-3.3 (m, 2H, H-1, H-5), 1.2-3.5 (m, 16H, restaliphate H), 7.0 (dd, 2H, Ar-H *ortho* to F, J ≈ 9), 7.88 (dd, 2H, Ar-H, *ortho* to CO, J ≈ 9); MS: m/z 340. Similarly, compounds **9-14** were prepared from the corresponding γ-chloropropyl-(4-substituted-phenyl)-sulphides. Their characterization data are given in Table 1.

9-[δ-*Hydroxy*-δ-(4-*fluorophenyl*)]*butyl*-9-*azabicyclo*[3.3.1]-*nonan*-3-*ol* (**8**)

Sodium borohydride (0.5 g, 13.2 mmole) was added in small portions to a stirred solution of **7** (1.0 g, 2.4 mmole) in absolute methanol (15 ml) and the stirring continued for 4 hr. The reaction mixture was concentrated to dryness and water (15 ml) added. The separated oil was extracted with chloroform (3 × 15 ml), the organic layer dried (Na_2CO_3), concentrated and the residue was purified by silica gel column chromatography $CHCl_3$—MeOH (5%) as eluant to give pure **8**, yield 0.56 g (55.3%), IR(Neat): 3400, 2800, 1600, 1420, 1220, 1160, 1120, 1050, 960, 940, 840, 780, 680; PMR ($CDCl_3$): 2.2-2.45 (m, 2H, H-2, H-4 axial), 3.0 (pseudo-triplet, 2H, H-1, H-5), 4.21 (quintet, 1H, H-3), 4.45-4.7 (m, 1H, *H*-C(OH)C_6H_5), 6.9 (dd, 2H, Ar-H, *ortho* to F, J = 8), 7.27 (dd, 2H, Ar-H, *ortho* to CHOH, J = 8); MS: m/z 307 (M^+), oil.

1,3-*Diethyl* 2-*oximinoglutarate* (**21**)

A mixture of ethyl 1,3-diethyl acetonedicarboxylate (**20**, 2.02 g, 1.0 mmole), sodium acetate (12.3 g, 1.5 mmole) and hydroxylamine hydrochloride (10.42 g, 1.5 mmole) in methanol (30 ml) was stirred at 32° for 15 hr. The reaction mixture was concentrated, diluted with water (20 ml), extracted with $CHCl_3$ (2 × 15 ml), dried (Na_2SO_4) concentrated and purified by passing through a silica gel column, using chloroform-methanol (20%) as eluant to give **21**, yield 1.4 g (64.5%); IR(Neat): 3500, 3000, 1820, 1740, 1640, 1380, 1340, 1280, 1220, 1040, 900, 780, 690; PMR ($CDCl_3$): 1.2 (t, 6H, CH_3), 3.4 (s, 4H, CH_2), 4.2 (q, 4H, $O-CH_2-CH_3$), 7.2 (bs, 1H, OH, exchangeable with D_2O): MS: m/z 217 (M^+), oil.

1,3-*Diethyl* 2-*aminoglutarate* (**22**)

Raney nickel (0.1 g) was added to solution of **21** (0.217 g, 1 mmole) in ethanol (15 ml) and the reaction mixture was shaken with H_2 in a Parr apparatus at 50 psi for 12 hr at 32°. The reaction mixture was filtered and concentrated to give **22**, characterized as its hy-

drochloride, yield 0.10 g (49.3%); m.p. 84° (lit.[19] m.p. 83.5-84.5°).

1,3-*Diethyl* 3-[3-*diethylglutaryl*]*iminoglutarate* (**23**)

A mixture of **22** (0.20 g, 1.0 m mole) and **20** (0.202 g, 1.0 mmole) was refluxed for 4 hr. in benzene at 90°. The reaction mixture was concentrated and purified on silica gel column, using $CHCl_3$ as eluant to give **23**, yield = 0.09 g (52.2%): IR(Neat): 3400, 1720, 1650, 1370, 1200, 1040, 950, 840, 760, PMR(CCl_4): 1.2 (t, 12H, CH_3), 2.15 (d, 8H, CH_2), 3.0-3.6 (m, 1H, *CH*—N), 4.1 (q, 8H, O—CH_2—CH_3): MS: m/z 385 (M^+), oil.

1,3-*Diethyl* 2-*benzylaminoglutarate* (**26**)

A mixture of diethylglutaconate (**25**), 1.86g, 10.0 m mole) and benzylamine (0.93 g, 5.0 m mole) in absolute ethanol was stirred at 32° for 76 hr. The reaction mixture was concentrated to give **26**, which was purified on silica gel column using benzene as eluant, yield 0.62 g (24%) IR (Neat): 3300, 3000, 1740, 1550, 1460, 1380, 1260, 1200, 1100, 1040, 820, 760, 700, PMR ($CDCl_3$): 1.2 (t, 6H, CH_3), 2.52 (d, 4H, CH_2—$CO_2C_2H_5$), 3.25-3.55 (m, 1H, NH_2—*CH*), 3.75 (s, 2H, $CH_2-C_6H_5$), 4.1 (q, 4H, CO_2—CH_2—CH_3), 7.2 (bs, 5H. Ar-H), oil

1,3-*Diethyl* 2-*aminoglutarate* (**22**)

Method A—A mixture of **26** (0.293 g, 1 mmole) and Pd/C (0.1g) in ethanol (10 ml) was shaken in a Parr apparatus under the hydrogen at 60 psi and 30° for 6 hr. The reaction mixture was filtered and the filtrate was concentrated to give **22**, characterized as its hydrochloride, yield 0.12 g (86.6%), m.p. 82° (lit.[19] m.p. 83.5-84.5°).

Method B—It was prepared from 1,3-diethyl glutaconate (**25**, 1.5g, 8.06 mmole) and ethanolic ammonia, according to literature method, yield 1.26g (77%), m.p. 83° (lit.[19] m.p. 83.5-84.5°).

N,N-bis(1,3-*diethylglutaryl*)*amine* (**24**)

A mixture of **22** (1.86 g, 10 mmole), **25** (2.03 g, 10 mmole) and triethylamine (0.4 ml) was kept in a stoppered flask at 32° for 20 days. The reaction mixture was extracted with HCl (50%, 4 × 20 ml) and the HCl extract basified with ammonia solution. The separated oil was extracted with $CHCl_3$ (3 × 15 ml), dried (Na_2SO_4) and concentrated to give **24**, yield 1.5 g (38.6%); IR (Neat): 3500, 3000, 1740, 1520, 1450, 1320, 1300, 1260, 1020, 960, 860, 740, 720; PMR($CDCl_3$): 1.2(t, 12H, CH_3), 2.5 (d, 8H, CH_2—$CO_2C_2H_5$), 3.2-3.55 (m, 2H, NH—*CH*), 4.2 (q, 8H, CO_2—CH_2-CH_3), 2.2 (bs, 1H, NH, exchangeable with D_2O); MS: m/z 389 (M^+), oil.

Diethyl 9-*azabicyclo*[3.3.1]*nonan*-3,7-*dione*-2,6-*dicarboxylate* (**28**)

A solution of **24** (0.25 g, 0.865 mmole) in absolute ethanol (0.002 ml) was added pulverised sodium (0.014 g, 0.61 mmole) in dry xylene (0.99 ml). The reaction mixture was refluxed at 140° for 24 hr and the separated solid was filtered to give **28** as an oil, which was purified by silica gel column chromatography, using $CHCl_3$-MeOH (5%) as eluant, yield 0.06 g (32.16%); IR(Neat): 3000, 1720, 1550, 1400, 1320, 1230, 1100, 1040, 950, 780, 700; PMR($CDCl_3$) 1.3(t, 6H, CH_3), 2.3-30 (m, 4H, H-4, H-8), 4.2(bs, 2H, H-2, H-6), 4.32-4.4(m, 2H, H-1, H-5), 4.45 (q, 4H, CH_2 CH_3), MS: m/z 297 $(M)^+$.

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Synthesis of oxadiazolyl-, thiadiazolyl- and triazolylindoles and indolylthiazolidinones

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Ethyl substituted indole-2-carboxylates (**1a-n**) are reacted with hydrazine hydrate to get the corresponding carbohydrazides (**2a-n**). These hydrazides are condensed with phenyl isothiocyanate to get 1-phenyl-3-(substituted indole-2′-carboxamido) thioureas (**3a-n**) which on treatment with iodine-potassium iodide solution, phosphoric acid and sodium hydroxide yield the substituted 2-(5′-phenylamino-1′, 3′, 4′-oxadiazol-2′-yl)indoles (**4a-n**), 2-(5′-phenylamino-1′, 3′, 4′-thiadiazol-2′-yl)indoles (**5a-n**) and 2-(5′-mercapto-4′-phenyl-1′, 2′, 4′-triazol-3′-yl)indoles (**6a-n**), respectively. Thioureas (**3a-n**) are also converted into 3-(substituted indole-2′-carboxamido)-2-phenylimino-4-thiazolidinones (**7a-n**) by treatment with chloroacetic acid in the presence of sodium acetate in acetic acid.

In view of the wide spectrum of activity associated with thiosemicarbazides,[1-4] substituted triazoles,[5,6] thiazolidinones[7-10] and 1,3,4-oxadiazol-5-ones[11], it was planned to synthesize some indole derivatives carrying the above biodynamic heterocyclic systems at position-2. The required substituted indole-2-carboxylates (**1a-1**) were obtained through Fischer indolization reaction. These esters were reacted with hydrazine hydrate to get indole-2-carbohydrazides (**2**) which on reaction with phenyl isothiocyanate in dry ethanol yielded 1-phenyl-3-(substituted indole-2′-carboxamido)thioureas (**3**). The latter (**3**) on treatment with iodine-potassium iodide solution, phosphoric acid and sodium hydroxide solution produced oxadiazoles (**4**), thiadiazoles (**5**) and triazoles (**6**), respectively (Schemes 1 and 2). The thioureas (**3**) were also treated with chloroacetic acid in the presence of sodium acetate in acetic acid to afford indolylthiazolidinones (**7**).

The IR‡ spectrum of **3b** exhibited absorptions due to NH/NH, C = O and C = S functions at 3320/3150, 1640 and 1160, respectively. Compound **4b** also exhibited characteristic absorption peaks at 1640/1600 and 3400/3250 due to C = N and NH/NH functions, respectively. The PMR‡ spectrum of **4b** showed the methyl protons at 2.5 and two NH protons at 10.2 and 11.4. The NH proton of oxadiazole nucleus appeared downfield at 11.4 due to deshielding effect of C − O in the α-position. The multiplet ranging from 6.6 to 7.5 was accounted for eight aromatic protons.

The thiourea **3b** when refluxed with 4% aq. sodium hydroxide for 1 hr afforded 5-chloro-3-methyl-2-(5′-mercapto-4′-phenyl-1′, 2′, 4′-triazol-3′-yl)indole (**6b**) which showed absorptions due to NH/NH and C = N functions at 3300/3175 and 1600, respectively in its IR spectrum. The PMR spectrum of **6b** showed methyl protons at 2.5 and NH proton of triazole nucleus at low field (10.9) due to the presence of adjacent − N = and − C = S groups. The integration indicated that the proton of indole NH had merged with aromatic protons. The aromatic cluster was observed at 7.8-6.5 which accounted for nine protons.

Compound **7a** showed peaks due to NH/NH, C = O/C = O and C = N functions at 3300/3400, 1720/1620 and 1580, respectively in its IR spectrum.

Biological activity

All the compounds synthesized in the present investigation were screened for their antibacterial activity against *E. coli*, *S. aureus* and *B. subtilis* and antifungal activity against *Candida utilis* and *Saccharomyces cerenisiae* by cup plate method. The compounds **3a,c,h,i, 4a,b,g,h, 5b,d,i** and **6b,f,g,i,j,k,l** were moderately active (20-30 mm) and **4i,j, 5a,k,l, 6c,h** and **7a** were highly active (< 30 mm). Rest of the compounds were inactive against *E. coli*. Compounds **3a,b,e, 4d,e, 5a,l** and **6d,e** exhibited high inhibition against *S.aureus* whereas **3d, 4a,l, 5i,j,k, 6a,b** and **7i** were moderately active and **4i,j, 5g** and **6i** were less active (12-20 mm); the remaining compounds were inactive against *S. aureus*. Compounds **6a,b,i,j** and **7e,h** were highly active whereas **3a,b,i,**

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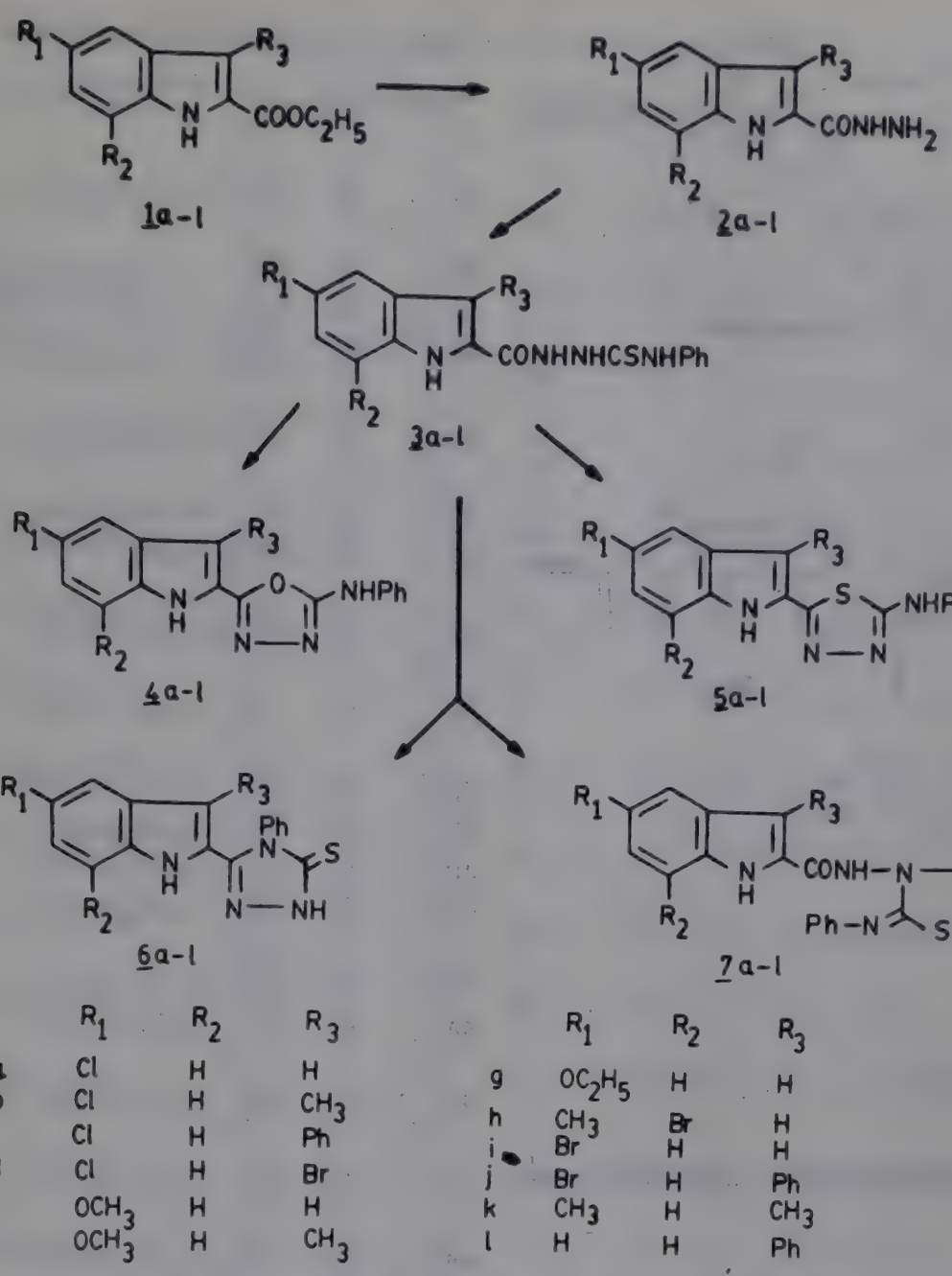
‡ IR ν_{max} in cm^{-1} and PMR chemical shifts in δ, ppm throughout this article.



	R_1	R_2	R_3		R_1	R_2	R_3
a	Cl	H	H	g	OC_2H_5	H	H
b	Cl	H	CH_3	h	CH_3	Br	H
c	Cl	H	Ph	i	Br	H	H
d	Cl	H	Br	j	Br	H	Ph
e	OCH_3	H	H	k	CH_3	H	CH_3
f	OCH_3	H	CH_3	l	H	H	Ph

Scheme 1

4b,l, 5k,l, 6d,e and **7a** were moderately active against *B. subtilis* and the rest of the compounds were either less active or inactive against the same organism.

Many of the compounds were found to be either less active or inactive against *Candida utilis* and *Saccharomyces cerenisiae*. Compounds **4d,i, 5a,b, 6c,d,h,i** and **7b** were highly active whereas **4b,c, 5e,g,k, 6a,e,g,k** and **7e**, were moderately active against *Candida utilis*. Compounds **4b,c, 6a,b** and **7d** were highly active and **4h,i, 5a** and **6e,g** were moderately active against *Saccharomyces cerenisiae*.

Experimental Procedure

All melting points reported are uncorrected. IR spectra were recorded in nujol on a Perkin-Elmer 297 IR spectrophotometer and PMR spectra in DMSO-d_6 on a Varian EM-390 spectrometer using TMS as internal standard.

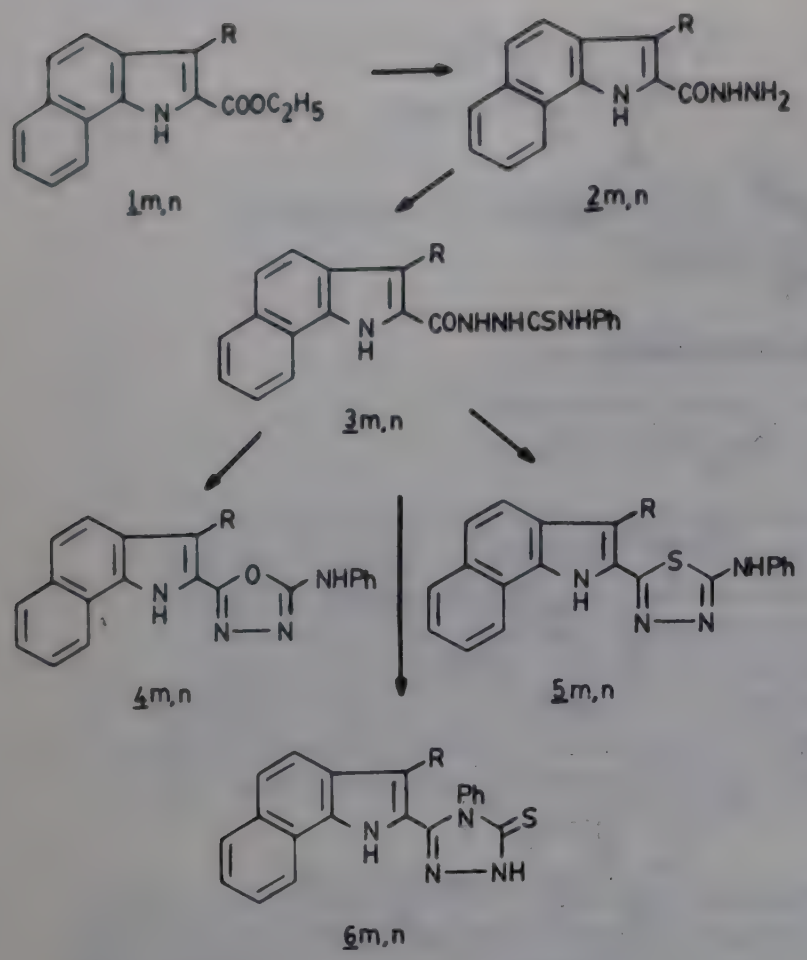
Ethyl substituted indole-2-carboxylates[12,13] and substituted indole-2-carbohydrazides[13,14] were prepared according to the literature methods.

1-Phenyl-3-(substituted indole-2'-carboxamido)-thioureas (**3**)

To a suspension of the hydrazides (**2**, 0.01 mole) in ethanol (30 ml), phenyl isothiocyanate (0.01 mole) was added with stirring. The mixture was heated under reflux for 5 hr on a water-bath. The solvent was removed under reduced pressure and the residue cooled. The solid separated was collected and crystallized from an appropriate solvent (Table 1).

Substituted 2-(1', 3', 4'-*oxadiazol*-2'-yl)indoles (**4**)

To a solution of **3** (0.001 mole) in ethanol (30 ml), sodium hydroxide solution (0.8 ml, 2*N*) was added with cooling and shaking. Iodine in KI (5%) was then added to it with shaking till the colour of the iodine persisted under reflux and if necessary more iodine solution was added till the colour persisted and the solvent removed under reduced pressure. The residue was cooled and acidified with acetic acid (10%) to get the free oxadiazolylindoles (**4**). The solid, after filtration, was washed with water and then with carbon



Scheme 2

disulphide, and crystallized from a suitable solvent (Table 1).

Substituted 2-(1′, 3′, 4′-thiadiazol-2′-*yl*)*indoles* (**5**)

Compound **3** (0.001 mole) was added slowly with shaking to anhyd. orthophosphoric acid (4 ml) during 25 min. The mixture was heated in an oil-bath at 135° for 1 hr. The syrupy liquid was poured into ice cold water and the resultant solid (**5**) collected by filtration, washed with water, dried and crystallized from a suitable solvent (Table 1).

Substituted 2-(1′, 2′, 4′-triazol-3′-*yl*)*indoles* (**6**)

The thiourea **3** (0.001 mole) was suspended in aq. sodium hydroxide (3.3 ml, 4%) and the mixture refluxed slowly for 1 hr. The solution was treated with charcoal and filtered. The filtrate was cooled and acidified carefully with acetic acid (10%). The precipitate formed was collected by filtration, washed with water and the product (**6**) crystallized from a suitable solvent (Table 1).

3-(*Substituted indole-2′-carboxamido*)-2-*phenylimino*-4-*thiazolidinones* (**7**)

To a solution of **3** (0.005 mole) in acetic acid (7.5 ml), monochloroacetic acid (0.005 mole) and anhy-

Table 1 – Characterization data of the compounds synthesized

Compd	Yield (%)	m.p.* °C	Mol formula	Found (%) (Calc) C	H	N
3a	90	210(d)	$C_{16}H_{13}N_4OClS$	55.9	3.6	16.5
				(55.7	3.8	16.3)
3b[15]	95	258	$C_{17}H_{15}N_4OSCl$	—	—	—
3c[16]	95	220	$C_{22}H_{17}N_4OClS$	—	—	—
3d	82	216(d)	$C_{16}H_{12}N_4OClBrS$	45.6	3.0	13.3
				(45.3	2.8	13.2)
3e	85	195(d)	$C_{17}H_{16}N_4O_2S$	60.2	4.6	16.7
				(60.0	4.7	16.5)
3f[15]	97	210	$C_{18}H_{18}N_4O_2S$	—	—	—
3g	84	190(d)	$C_{18}H_{18}N_4O_2S$	61.3	5.0	16.0
				(61.0	5.1	15.8)
3h	91	207(d)	$C_{17}H_{15}N_4OSBr$	50.4	3.5	14.1
				(50.6	3.7	13.9)
3i	94	267	$C_{16}H_{15}N_4OBrS$	49.7	3.2	14.6
				(49.4	3.3	14.4)
3j[16]	90	215	$C_{22}H_{17}N_4OBrS$	—	—	—
3k[15]	85	245(d)	$C_{18}H_{18}N_4OS$	—	—	—
3l[16]	93	152	$C_{22}H_{18}N_4OS$	—	—	—
3m	80	170	$C_{21}H_{18}N_4OS$	67.5	5.0	15.1
				(67.4	4.8	15.0)
3n[16]	92	182	$C_{26}H_{20}N_4OS$	—	—	—
4a	65	307	$C_{16}H_{11}N_4OCl$	62.0	3.6	18.3
				(61.8	3.5	18.0)
4b	72	298	$C_{17}H_{13}N_4ClO$	62.6	3.9	17.5
				(62.9	4.0	17.3)
4c	80	255	$C_{22}H_{15}N_4OCl$	68.5	4.1	14.3
				(68.3	3.9	14.5)
4d	60	275	$C_{16}H_{10}N_4OBrCl$	49.4	2.9	14.5
				(49.3	2.6	14.4)
4e	75	250	$C_{17}H_{14}N_4O_2$	66.9	4.5	18.5
				(66.7	4.6	18.3)
4f	70	217	$C_{18}H_{16}N_4O_2$	67.8	5.2	17.3
				(67.5	5.0	17.5)
4g	73	260	$C_{18}H_{16}N_4O_2$	67.3	5.1	17.7
				(67.5	5.0	17.5)
4h	68	235	$C_{17}H_{13}N_4OBr$	55.5	3.8	15.4
				(55.3	3.5	15.2)
4i	65	316	$C_{16}H_{11}N_4OBr$	54.0	3.2	16.0
				(54.1	3.1	15.8)
4j	65	267	$C_{22}H_{15}N_4OBr$	61.5	3.3	13.3
				(61.3	3.5	13.0)
4k	67	287	$C_{18}H_{16}N_4O$	71.4	5.1	18.3
				(71.1	5.3	18.4)
4l	58	184	$C_{22}H_{16}N_4O$	75.2	4.4	16.1
				(75.0	4.6	15.9)
4m	65	162	$C_{21}H_{16}N_4O$	74.3	4.8	16.7
				(74.1	4.7	16.5)
4n	70	246	$C_{26}H_{18}N_4O$	77.9	4.7	14.1
				(77.6	4.5	13.9)

(*Contd.*)

Compd	Yield (%)	m.p.* °C	Mol formula	Found (%) (Calc) C	H	N
5a	70	243	$C_{16}H_{11}N_4SCl$	59.0 (58.8	3.6 3.4	17.5 17.2)
5b	73	180	$C_{17}H_{13}N_4SCl$	60.2 (60.0	3.5 3.8	16.6 16.5)
5c	80	198	$C_{22}H_{15}N_4SCl$	65.9 (65.6	3.8 3.7	14.1 13.9)
5d	64	184(d)	$C_{16}H_{10}N_4SBrCl$	47.6 (47.6	2.3 2.5	13.6 13.8)
5e	70	165	$C_{17}H_{14}N_4SO$	63.7 (63.4	4.5 4.3	17.5 17.4)
5f	75	158	$C_{18}H_{16}N_4SO$	64.6 (64.3	4.5 4.8	16.8 16.7)
5g	71	240	$C_{18}H_{16}N_4SO$	64.5 (64.3	5.0 4.8	16.6 16.7)
5h	60	195	$C_{17}H_{13}N_4SBr$	53.1 (53.0	3.6 3.4	14.4 14.5)
5i	57	185	$C_{16}H_{11}N_4SBr$	51.9 (51.8	3.3 3.0	15.4 15.1)
5j	62	154	$C_{22}H_{15}N_4SBr$	59.3 (59.1	3.5 3.4	12.6 12.5)
5k	55	(162(d)	$C_{18}H_{16}N_4S$	67.7 (67.5	5.1 5.0	17.3 17.5)
5l	50	118(d)	$C_{22}H_{16}N_4S$	71.6 (71.7	4.5 4.3	15.4 15.2)
5m	60	145	$C_{21}H_{16}N_4S$	71.3 (74.6	4.2 4.3	13.6 13.4)
5n	68	193	$C_{26}H_{18}N_4S$	74.3 (74.6	4.2 4.3	13.6 13.4)
6a	75	320	$C_{16}H_{11}N_4SCl$	59.1 (58.8	3.2 3.4	17.0 17.2)
6b	71	322	$C_{17}H_{13}N_4SCl$	60.2 (60.0	3.9 3.8	16.8 16.5)
6c	85	180	$C_{22}H_{15}N_4SCl$	65.9 (65.6	3.5 3.7	14.1 13.9)
6d	50	215	$C_{16}H_{10}N_4SBrCl$	47.5 (47.4	2.7 2.5	13.7 13.8)
6e	70	275	$C_{17}H_{14}N_4SO$	63.7 (63.4	4.4 4.3	17.6 17.4)
6f	68	273	$C_{18}H_{16}N_4SO$	64.5 (64.3	5.0 4.8	16.9 16.7)
6g	65	280	$C_{18}H_{16}N_4SO$	64.1 (64.3	4.7 4.8	16.8 16.7)
6h	74	296	$C_{17}H_{13}N_4SBr$	53.1 (53.0	3.6 3.4	14.7 14.5)
6i	55	323	$C_{16}H_{11}N_4SBr$	52.1 (51.8	3.2 3.0	15.4 15.1)
6j	69	192	$C_{22}H_{15}N_4SBr$	59.2 (59.1	3.3 3.4	12.7 12.5)
6k	75	190	$C_{18}H_{16}N_4S$	67.8 (67.5	5.2 5.0	17.3 17.5)
6l	66	165(d)	$C_{22}H_{16}N_4S$	71.9 (71.7	4.2 4.3	15.3 15.2)
6m	63	205	$C_{21}H_{16}N_4S$	70.9 (70.8	4.7 4.5	15.9 15.7)
6n	70	172	$C_{26}H_{18}N_4S$	74.8 (74.6	4.4 4.3	13.2 13.4)
7a	60	238	$C_{18}H_{13}N_4O_2SCl$	56.4 (56.2	3.7 3.4	14.8 14.6)
7d	65	215	$C_{18}H_{12}N_4O_2SBrCl$	46.8 (46.6	2.8 2.6	12.3 12.1)
7e	70	155	$C_{19}H_{16}N_4O_3S$	60.1 (60.0	4.4 4.2	14.8 14.7)
7h	68	132	$C_{19}H_{15}N_4O_2SBr$	51.7 (51.5	3.5 3.4	12.8 12.6)
7i	60	260	$C_{18}H_{13}N_4O_2SBr$	50.6 (5.3	3.2 3.0	13.3 13.1)

* Solvents for crystallization were: Ethanol for **4a-d,f,h,k, 5g, 6a,b,d-i;** aq. ethanol for **4l-n, 5b,i, 6c,j-n;** benzene for **5c-f; j-n; 7a-j;** ethyl acetate for **4e,g;** and ethanol + benzene for **5a.**

drous sodium acetate (0.005 mole) were added. The reaction mixture was refluxed for 8 hr, cooled, poured onto crushed ice. The separated solid was filtered, washed thoroughly with water, dried and crystallized from a suitable solvent to give **7** (Table 1).

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Heterocyclic systems containing bridgehead nitrogen atom: Syntheses of thiazolo[3,2-*a*]benzimidazol-3(2*H*)-ones and thiazolo[3,2-*a*]benzimidazoles

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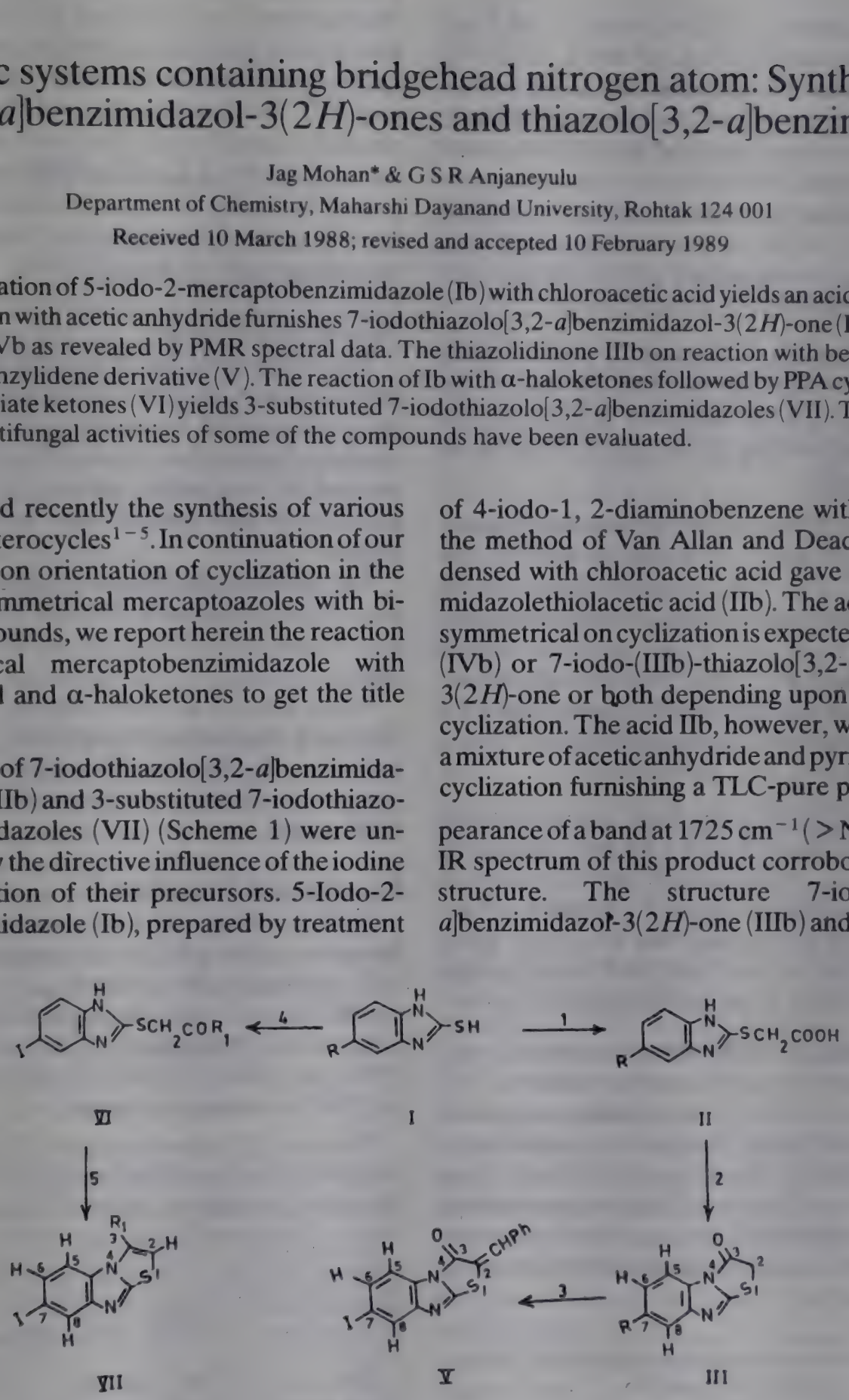
Condensation of 5-iodo-2-mercaptobenzimidazole (Ib) with chloroacetic acid yields an acid (IIb) which on cyclization with acetic anhydride furnishes 7-iodothiazolo[3,2-*a*]benzimidazol-3(2*H*)-one (IIIb) and not the isomer IVb as revealed by PMR spectral data. The thiazolidinone IIIb on reaction with benzaldehyde yields the benzylidene derivative (V). The reaction of Ib with α-haloketones followed by PPA cyclization of the intermediate ketones (VI) yields 3-substituted 7-iodothiazolo[3,2-*a*]benzimidazoles (VII). The antibacterial and antifungal activities of some of the compounds have been evaluated.

We have reported recently the synthesis of various thiazole fused heterocycles[1-5]. In continuation of our earlier studies[3,6] on orientation of cyclization in the reaction of unsymmetrical mercaptoazoles with bifunctional compounds, we report herein the reaction of unsymmetrical mercaptobenzimidazole with chloroacetic acid and α-haloketones to get the title compounds.

The syntheses of 7-iodothiazolo[3,2-*a*]benzimidazol-3(2*H*)-one (IIIb) and 3-substituted 7-iodothiazolo[3,2-*a*]benzimidazoles (VII) (Scheme 1) were undertaken to study the directive influence of the iodine atom on cyclization of their precursors. 5-Iodo-2-mercaptobenzimidazole (Ib), prepared by treatment of 4-iodo-1, 2-diaminobenzene with CS_2 following the method of Van Allan and Deacon[7], when condensed with chloroacetic acid gave 5-iodo-2-benzimidazolethiolacetic acid (IIb). The acid IIb being unsymmetrical on cyclization is expected to give 6-iodo- (IVb) or 7-iodo-(IIIb)-thiazolo[3,2-*a*]benzimidazol-3(2*H*)-one or both depending upon the direction of cyclization. The acid IIb, however, when heated with a mixture of acetic anhydride and pyridine underwent cyclization furnishing a TLC-pure product. The appearance of a band at 1725 cm^{-1} ($>N-\overset{|}{C}=O$) in the IR spectrum of this product corroborated the cyclic structure. The structure 7-iodothiazolo[3,2-*a*]benzimidazol-3(2*H*)-one (IIIb) and not the 6-iodo-



SCHEME 1

isomer (IVb) was assigned to it on the basis of PMR spectral data.

The assignments of the PMR signals to C_5-H, C_6-H and C_8-H in IIIb and to C_5-H, C_7-H and C_8-H in IVb were based on calculations by taking into consideration the deshielding and shielding effects of iodine atom (-0.40 δ for *ortho*-proton and +0.26 δ for *meta*-proton)[8] on chemical shifts of the corresponding protons of the parent compounds (IIIa-IVa). In the PMR spectrum ($CDCl_3$) of IIIa (or IVa) the signals at δ7.89, 7.39 and 7.69 were assigned to C_5-H, C_6-H (or C_7-H) and C_8-H respectively.

Interestingly enough, C_5-H and C_8-H are farthest downfield in IVb and IIIb respectively due to the deshielding effect of the carbonyl group and the shielding and deshielding effects of iodine atom on *meta/ortho*-protons.

If the structure IIIb is correct, the calculated chemical shifts for C_5-H and C_8-H would be δ7.63 (7.89-0.26) and 8.09 (7.69 + 0.40) respectively (set-A). On the other hand, if structure IVb is correct, the calculated values for C_5-H and C_8-H would be δ8.29 (7.89 + 0.40) and 7.43 (7.69-0.26) respectively (set-B). The observed and calculated chemical shifts for the aromatic protons of structures IIIb and IVb are given in Table 1.

The observed signals in the PMR spectrum of the cyclized product (from IIb) at δ7.54 and 8.09 may be due to C_5-H and C_8-H respectively (set-C) if structure IIIb is correct, or may be due to C_8-H and C_5-H respectively (set-D) if structure IVb is correct. Since set-A is very close to set-C and set-B does not tally with set-D (see Table 1) the structure IIIb is correct.

The thiazolidinone (IIIb) when condensed with benzaldehyde gave benzylidenethiazolidinone (V). The structures of IIIb and V were further supported by their IR spectral data. The parent thiazolidinone (III) showed carbonyl absorption at 1725 cm^{-1} but the unsaturation at 2-position, being conjugated with carbonyl at 3-position in V, produced a bathochromic shift[9] as expected; the carbonyl absorption appeared at 1700 cm^{-1} in V.

Table 1—Observed and calculated chemical shifts for aromatic protons in IIIb and IVb

Structure	C_5-H		C_8-H	
	Calc.	Obs.	Calc.	Obs.
IIIa-IVa (Parent)	—	7.89	—	7.69
IIIb	7.63	7.54	8.09	8.09
IVb	8.29	8.09	7.43	7.54

5-Iodo-2-mercapto-benzimidazole (Ib), when treated with α-haloketones, yielded the ketones (VI; characterized by νC=O at 1675 cm^{-1} in their IR spectra) which underwent facile cyclization with polyphosphoric acid to give the corresponding TLC-pure VII. The absence of νC=O in IR spectra of the products corroborated the cyclic structure. The signal at δ6.80 (1H, s, C_2-H) in PMR spectra further supported the cyclic structure. Assignment of the structure VII to the cyclized products was, however, based on analogy with the structure IIIb.

Antimicrobial activity

The compounds IIIb, V and VII (R_1 = *p*-Cl-C_6H_4-) were screened for their antibacterial activity against the gram-positive *Staphylococcus aureus* and gram-negative *Escherichia coli* and *Pseudomonas aeruginosa* and for their antifungal activity against *Candida albicans* by neat samples and serial plate dilution method[10].

The minimum inhibitory concentration (MIC) values of the compounds IIIb and V against *S. aureus* were found to be 500 μg/ml and 250 μg/ml respectively.

When treated as neat samples, the compounds IIIb and V showed activity against *E. Coli*, *Ps.aeruginosa* and *C.albicans*; the MIC values of the compounds showing neat activity may be greater than 1000 μg/ml.

Experimental Procedure

Melting points are uncorrected. TLC was performed on silica-gel G plates using acetone-benzene (1:3) as irrigant. IR spectra (ν_{max} in cm^{-1}) were recorded in nujol on a Backman IR-20 spectrophotometer and PMR spectra (chemical shift in δ, ppm) in $CDCl_3$ on a Perkin-Elmer 90 MHz spectrometer using TMS as internal reference.

Thiazolo[3,2-*a*]benzimidazol-3(2*H*)-one (IIIa) and 5-iodo-2-mercapto-benzimidazole (Ib) were synthesized according to reported methods[7,11].

Ib: m.p. 274° (Found: N, 10.6; S, 11.8. $C_7H_5N_2SI$ requires N, 10.2; S, 11.6%); IR: 810, 870 (1, 2, 4-trisubstituted benzene ring), 1180 (C=S), 1625 (C=N), 2450 (S—H), 3390 (N—H stretching).

IIIa: m.p. 181° (lit.[11], m.p. 181°); PMR: 7.39 (2H, m, C_6-H and C_7-H), 7.69 (1H, m, C_8-H), 7.89 (1H, m, C_5-H).

5-Iodo-2-benzimidazolethiolacetic acid (IIb)

A mixture of Ib (2.76 g, 0.01 mole), chloroacetic acid (0.95 g, 0.01 mole) and anhyd. sodium acetate (0.82 g, 0.01 mole) in anhyd. ethanol (100 ml) was refluxed for 5 hr, concentrated and cooled to room tempera-

ture. The solid thus separated was filtered, washed with water and crystallised from ethanol as light yellow flakes, m.p. 202°, yield 2.1g (63%) (Found: N, 8.7; S, 9.3. $C_9H_7N_2O_2SI$ requires N, 8.4; S, 9.6%); IR: 810, 870 (1,2,4-trisubstituted benzene ring), 1500 (C—N stretching), 1595, 1610 (C=N), 2575, 2650 (COOH), 3375 (N—H stretching).

7-Iodothiazolo[3,2-*a*]*benzimidazol*-3(2*H*)-*one* (*IIIb*)

A mixture of IIb (1.0 g), acetic anhydride (1.0 ml) and pyridine (3.0 ml) was heated on a steam-bath for 5 min, cooled to room temperature and kept overnight. The orange red needles thus separated were filtered, washed with water and crystallised from ethanol to give orange needles, m.p. 175°, yield 0.6 g (63%) (Found: C, 34.4; H, 1.8; N, 9.3; S, 10.8. $C_9H_5N_2OSI$ requires C, 34.2; H, 1.6; N, 8.9; S, 10.6%); IR: 820, 875 (1,2,4-trisubstituted benzene ring), 1490 (C—N stretching), 1600 (C=N), 1725 (C=O); PMR: 4.51 (2H, s, CH_2), 7.54 (1H, d, C_5-H, $J_{5,6}$ = 9 Hz), 7.79 (1H, dd, C_6-H, $J_{5,6}$ = 9Hz, $J_{6,8}$ = 2.25 Hz), 8.09 (1H, d, C_8-H, $J_{6,8}$ = 2.25 Hz).

2-Benzylidene-7-iodothiazolo[3,2-*a*]*benzimidazol*-3(2*H*)-*one* (*V*)

A mixture of IIIb (1.58g, 0.005 mole), benzaldehyde (0.53 g, 0.005 mole) and anhyd. sodium acetate (0.41g, 0.005 mole) in gl. acetic acid (25 ml) was refluxed on a heating mantle for 3 hr. The yellow solid that separated on cooling, was filtered, washed with water and crystallised from ethanol to give bright yellow flakes, m.p. 210°, yield 1.20g (59%) (Found: N, 7.2; S, 8.2. $C_{10}H_9N_2OSI$ requires N, 6.9; S, 7.9%); IR: 670, 710, 750, 810, 875 (1,2,4-trisubstituted and monosubstituted benzene rings), 1490 (C—N stretching), 1605 (C=N), 1700 (C=O).

5-Iodo-2-phenacylthiobenzimidazole (VI_1, $R_1 = C_6H_5-$)

A mixture of Ib (1.38 g, 0.005 mole) and phenacyl chloride (0.78 g, 0.005 mole) in anhyd. ethanol (50 ml) was heated under reflux for 4 hr, cooled to room temperature and neutralized with aq. K_2CO_3 solution. The solid thus obtained was crystallized from ethanol as faint yellow shining flakes, m.p. 172°, yield 1.20 g (61%) (Found: N, 7.4; S, 8.4. $C_{15}H_{11}N_2OSI$ requires N, 7.1; S, 8.1%); IR: 830, 870 (1,2,4-trisubstituted benzene ring), 1590, 1610 (C=N), 1675 (C=O), 3400 (broad NH).

Other derivatives of VI prepared similarly were:

VI_2 (R_1 = *p*-Cl—C_6H_4—): Obtained from Ib and *p*-Cl-$C_6H_4COCH_2Br$ in 56% yield, m.p. 232° (Found: N, 6.2; S, 7.8. $C_{15}H_{10}N_2OSClI$ requires N, 6.5; S, 7.5%): IR: 810, 870 (1,2,4-trisubstituted and *p*-disubstituted benzene rings), 1600, 1625 (C=C and C=N), 1675 (C=O), 3260 (NH).

VI_3 (R_1 = *p*-Br-C_6H_4—): Obtained from Ib and *p*-Br-C_6H_4—$COCH_2Br$ in 55% yield, m.p. 192° (Found N, 6.3; S, 7.2. $C_{15}H_{10}N_2OSBrI$ requires N, 5.9; S, 6.8%); IR: 815, 880 (1,2,4-trisubstituted and *p*-disubstituted benzene rings), 1575, 1600 (C=N), 1675 (C=O), 3250 (NH).

7-Iodo-3-phenylthiazolo[3,2-*a*]*benzimidazole* (VII_1, $R_1 = C_6H_5-$)

A mixture of the ketone VI_1 (1g), P_2O_5 (4g) and H_3PO_4 (3 ml) was heated in an oil-bath at 150° for 4 hr, cooled, poured into water and neutralized with K_2CO_3. The solid so obtained was crystallized from ethanol as colourless needles, m.p. 135°, yield 0.4 g (42%) (Found: C, 48.2; H, 2.6; N, 7.2; S, 8.1. $C_{15}H_9N_2SI$ requires C, 47.9; H, 2.4; N, 7.5; S, 8.5%); IR: 680, 750, 820, 860 (1,2,4-trisubstituted and monosubstituted benzene rings), 1600, 1640 (C=C and C=N); PMR: 6.80 (1H, s, C_2—H), 7.16-8.05 (8H, m, aromatic protons).

Other thiazolo-*s*-benzimidazoles (VII) prepared similarly were:

VII_2 (R_1 = *p*-Cl—C_6H_4—): Obtained from VI_2 in 47% yield, m.p. 196° (EtOH) (Found: N, 7.1; S, 8.1. $C_{15}H_8N_2SClI$ requires N, 6.8; S, 7.8%); IR: 810, 835, 880 (1,2,4-trisubstituted and *p*-disubstituted benzene rings), 1540 (C—N stretching), 1600, 1640 (C=C and C=N); PMR: 6.93 (1H, s, C_2-H), 7.35-8.25 (7H, m, aromatic protons).

VII_3 (R_1 = *p*-Br-C_6H_4-): Obtained from VI_3 in 37% yield, m.p. 198° (EtOH) (Found: N, 6.5; S, 7.4. $C_{15}H_8N_2SBrI$ requires N, 6.2; S, 7.0%); IR: 810, 835, 870 (1,2,4-trisubstituted and *p*-disubstituted benzene rings), 1540 (C—N), 1610 (C=N); PMR: 6.85 (1H, s, C_2—H), 7.30-8.15 (7H, m, aromatic protons).

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Alkali catalyzed thermal cyclization of 1-substituted and 1,6-disubstituted-2,5-dithiobiureas: Formation of 1,2,4-triazolidine-3,5-dithiones and/or 1,3,4-thiadiazoline-5-thiones

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Alkali catalyzed thermal cyclization of 1-alkyl and 1,6-dialkyl-2,5-dithiobiureas (I,R = alkyl, R′ = H and R = R′ = alkyl) results in the formation of 4-alkyl-1,2,4-triazolidine-3,5-dithiones (V) (alkyl = Me or Et) and 2-alkylamino-Δ^2-1,3,4-thiadiazoline-5-thiones (VI) (alkyl = *n*-Pr or *n*-Bu). Under the same conditions, 1-alkyl-6-aryl-2,5-dithiobiureas (I,R = alky, R′ = aryl) give 2-arylamino-Δ^2-1,3,4-thiadiazoline-5-thiones (IX) (alkyl = Me, Et, *n*-Pr or *n*-Bu) and 4-alkyl-1,2,4-triazolidine-3,5-dithiones (V) also when the alkyl groups are Me or Et.

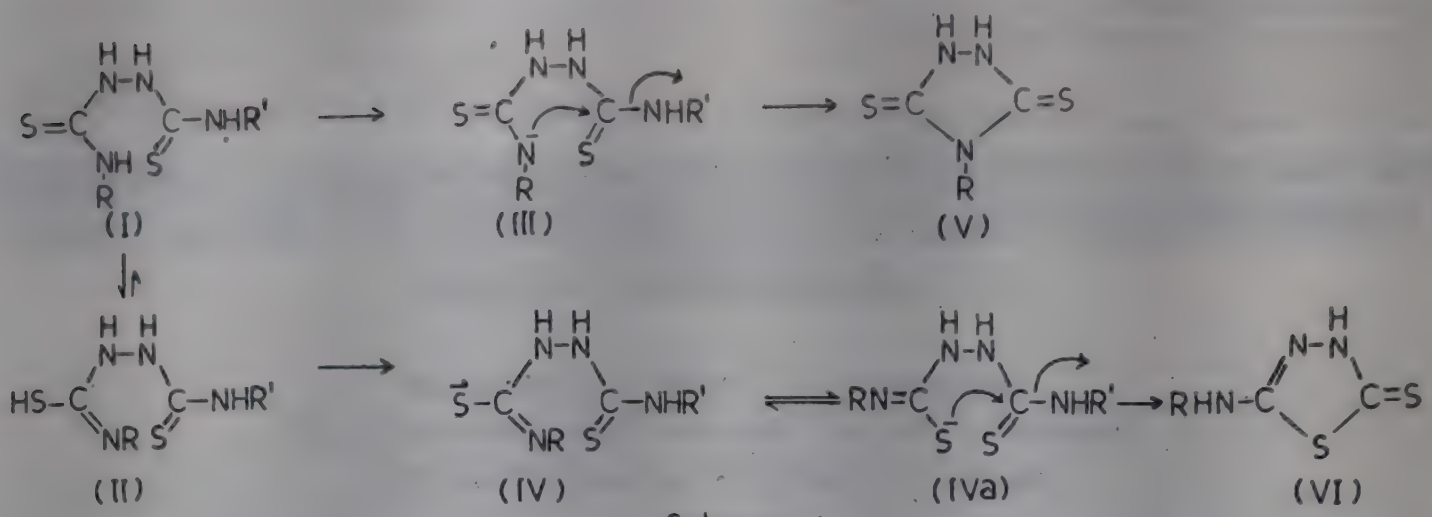
1,2,4-Triazoles and 1,3,4-thiadiazoles continue to draw the attention of synthetic organic chemists due to their varied pharmacological properties. As early as 1924, Fromm and coworkers[1] reported that when 1,6-diphenyl-2,5-dithiobiurea was heated in the presence of alkali, the sole product obtained was 4-phenyl-3-phenylamino-Δ^2-1,2,4-triazoline-5-thione, while Dubenko and Pelkis[2] reported the formation of 4-alkyl/aryl-1,2,4-triazolidine-3,5-dithiones, during alkali-catalyzed thermal cyclization of 1,6-dialkyl/aryl-2,5-dithiobiureas. In order to find out the effect of alkyl groups at 1-and/or 6-positions during cyclization, the reactions of several 1-alkyl-1,6-dialkyl- and 1-alkyl-6-aryl-2,5-dithiobiureas have now been examined.

Alkali-catalyzed thermal cyclizations of 1-ethyl/methyl-2,5-dithiobiureas (I) led to two products which were characterized as 4-ethyl/methyl-1,2,4-triazolidine-3,5-dithiones (V), respectively (see Scheme 1). They formed di S-benzyl derivatives when treated with benzyl chloride in presence of alkali indicating the presence of two enolisable thione groupings. 1-*n*-Butyl/*n*-propyl-2,5-dithiobiureas formed 2-*n*-butyl/*n*-propylamino-Δ^2-1,3,4-thiadiazoline-5-thiones (VI) which formed mono S-benzyl derivatives showing that only one enolisable thione group is present in the product (VI).

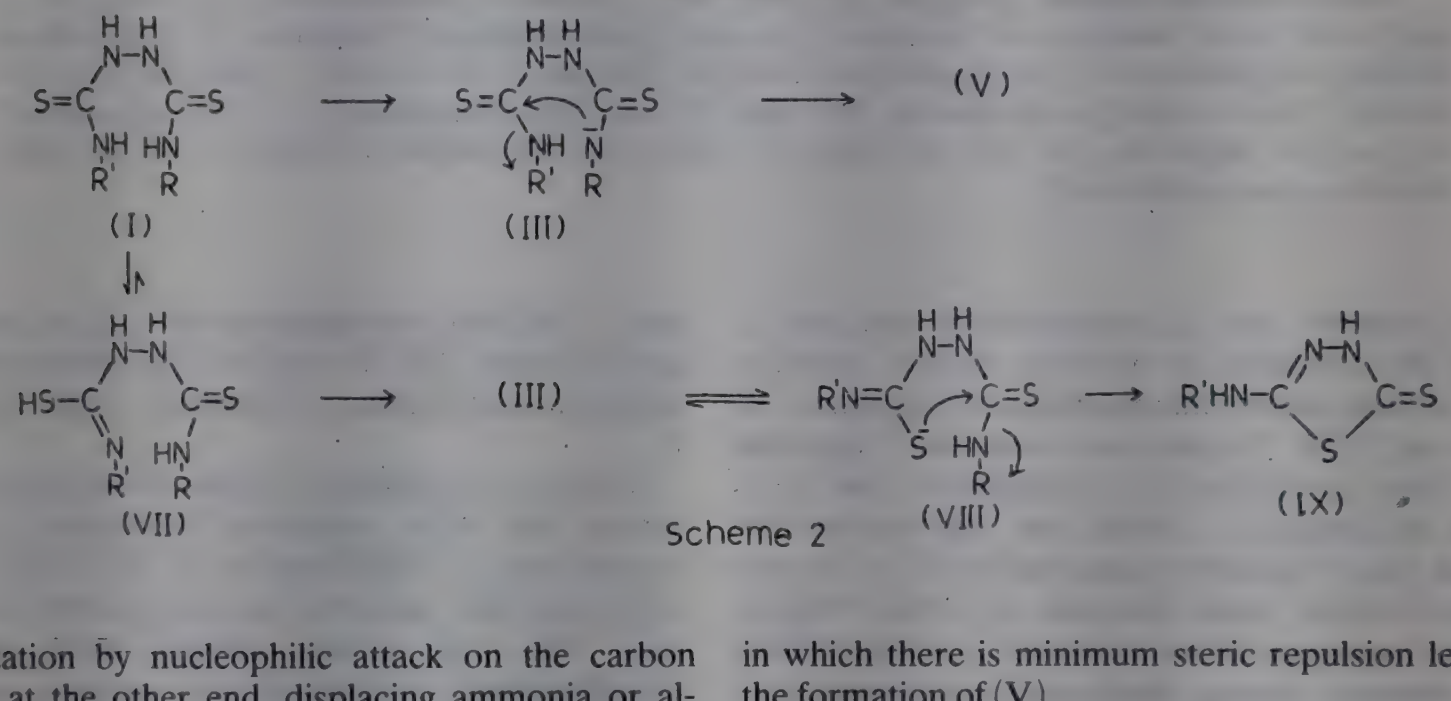
In the alkali-catalyzed thermal cyclization of 1,6-dialkyl-2,5-dithiobiureas (I, R = R′ = alkyl), it was observed that when both the alkyl groups are ethyl/methyl, 4-ethyl/methyl-1,2,4-triazolidine-3,5-dithione (V) was formed, respectively by the elimination of ethyl/methylamine. In the case of 1,6-di-*n*-butyl/*n*-propyl-2,5-dithiobiureas, the products were 2-*n*-butyl/*n*-propylamino-Δ^2-1,3,4-thiadiazoline-5-thiones (VI), formed by the elimination of *n*-butyl/*n*-propylamine, respectively (see Scheme 1).

In view of the different modes of cyclization observed with alkyl substituted derivatives, a few 1-alkyl-6-aryl-2,5-dithiobiureas (I, R = alkyl, R′ = aryl) were also subjected to this cyclization reaction. The aryl groups chosen were phenyl, 4-methylphenyl, *p*-chlorophenyl, *p*-anisyl and *p*-phenetyl. Keeping the aryl groups the same, alkyl groups (methyl, ethyl, *n*-propyl and *n*-butyl) were varied. When the alkyl group was methyl or ethyl, two products were obtained which could be separated by column chromatography over silica gel. One of the products was identified as 2-arylamino-Δ^2-1,3,4-thiadiazoline-5-thione (IX) formed by the intramolecular nucleophilic attack of the sulphur atom near the arylamino group displacing alkylamine (Scheme 2). It formed a mono S-benzyl derivative and its identity was proved by comparison with an authentic sample[3]. The other product was identified as 4-ethyl/methyl-1,2,4-triazolidine-3,5-dithione (V). When the alkyl group was *n*-propyl or *n*-butyl, the sole product obtained was characterized as 2-arylamino-Δ^2-1,3,4-thiadiazoline-5-thione (IX). It was presumably formed by the elimination of alkylamine (Scheme 2).

We believe that dithiobiureas (I,R = alkyl, R′ = H or R = R′ = alkyl) dissolved in minimum quantity of aq sodium hydroxide, exist in the tautomeric form (II). The anions III and IV respectively formed from I and II carry a negative charge on the nitrogen and sulphur atoms and these can undergo



Scheme 1



Scheme 2

cyclization by nucleophilic attack on the carbon atom at the other end, displacing ammonia or alkylamine.

The formation of different products during cyclization can be explained on the basis of the electronic and the steric effects of the alkyl groups. When the alkyl groups are methyl or ethyl (I, R = Me or Et, R′ = H and I, R = R′ = Me or Et), the electronic effect of the alkyl group is the major factor governing the mode of cyclization and the attack by the nitrogen atom carrying the alkyl substituent always occurs resulting in the formation of 4-ethyl/methyl-1,2,4-triazolidine-3,5-dithiones (V) (Scheme 1).

While going from methyl, ethyl, *n*-propyl to *n*-butyl, the inductive effect increases in the order given. But the steric effect of the alkyl group also increases and it exerts some influence on the mode of cyclization (see Scheme 1).

When 1-alkyl-6-aryl-2,5-dithiobiurea (I,R = alkyl, R′ = aryl) is dissolved in minimum quantity of aq sodium hydroxide, it could give rise to VIII which is the tautomeric form of III, where R = alkyl and R′ = H or alkyl. VIII, on cyclization with the elimination of amine would give 2-arylamino-Δ^2-1,3,4-thiadiazoline-5-thione (IX). The anion III in which there is minimum steric repulsion lead to the formation of (V).

Experimental Procedure

The purity of the products in each case was ascertained by TLC. All the melting points reported are uncorrected. Satisfactory elemental analysis were obtained for all the compounds reported herein.

Alkali-catalyzed thermal cyclization of 1-*alkyl*-2,5-*dithiobiureas* (*I*,*R* = *alkyl*, *R′* = *H*): *Formation of* 4-*alkyl*-1,2,4-*triazolidine*-3,5-*dithione* (*V*)

In a typical experiment a solution of I (16.4 g, 0.1 mole) in minimum quantity of aq sodium hydroxide (2%, 20 ml) was heated on a water-bath for 2 hr with continuous bubbling of air through the solution. The gaseous product issuing out was absorbed in an ethereal solution of phenyl isothiocyanate. A white crystalline solid started separating in the ether layer. The precipitated solid in the ether layer was collected and crystallized from aq ethanol. m.p. 154° (lit.[4], m.p. 154°).

The alkaline reaction mixture on cooling followed by acidification afforded a cream white precipitate, which was cooled, washed and dried.

Crystallization from aq ethanol yielded pale cream needle shaped crystals of V (yield 8.8 g, 60%), m.p. 240° (V, R = Me) (lit.[5], m.p. 240°).

Other 1-alkyl and 1,6-dialkyl-2,5-dithiobiureas were similarly cyclized. Their characterization data are given in Table 1.

Alkali-catalyzed thermal cyclization of 1-*alkyl*-6-*aryl*-2,5-*dithiobiureas* (*I*, *R* = *alkyl*, *R'* = *aryl*): *Formation of* 2-*arylamino*-Δ^2-1,3,4-*thiadiazoline*-5-*thiones* (*IX*) *and* 4-*alkyl*-1,2,4-*triazolidine*-3,5-*dithione* (*V*)

In a typical experiment 1-methyl-6-phenyl-2,5-dithiobiurea (9.6 g, 0.04 mole), dissolved in minimum quantity of aq sodium hydroxide (2%, 20 ml) was heated on a boiling water-bath for 2 hr. Initially a stream of nitrogen gas was passed through the solution to displace any volatile material produced. The outcoming gas was passed through an ethereal solution of phenyl isothiocyanate. A white precipitate was separated in the ethereal solution. The flushing of the reaction mixture with nitrogen was stopped when no more white solid separated. Steam was then passed through the reaction mixture to distill out any arylamine formed. The steam-distillate was extracted with ether and was mixed with phenyl isothioçyanate. On keeping, white plate like crystals separated. Both the white products were separately examined. The former was identified as 1-methyl-3-phenylthiourea, m.p. 113° (lit.[4], m.p. 113°) and the latter as 1,3-diphenylthiourea, m.p. 154° (lit.[4], m.p. 154°).

The alkaline reaction mixture was concentrated, chilled in ice and neutralized with conc. hydrochloric acid, when a pale yellow precipitate was obtained. It was collected, washed with cold water and dried. TLC examination showed the presence of two components. They were separated by chromatography over a column of silica gel. Elution with benzene afforded a product which crystallized from ethanol as lemon yellow needles. It was identified as 2-phenylamino-Δ^2-1,3,4-thiadiazoline-5-thione (IX) (yield 4.3 g, 52%), m.p. 228° (lit.[3], m.p. 219°).

Further elution of the column with benzene-chloroform mixture (60:40, v/v) yielded another product which crystallized from ethanol as shining pale yellow needles. It was identified as 4-methyl-1,2,4-triazolidine-3,5-dithione (V, R = Me).

Table 1 – Alkali-catalyzed thermal cyclization of 1-alkyl, 1,6-dialkyl- and 1-alkyl-6-aryl-2,5-dithiobiurea (I)

Dithiobiurea I			V*			VI or IX*			
R	R'	Mol formula	Yield %	m.p. °C	Lit.[5] m.p. °C	Mol formula	Yield %	m.p. °C	Lit.[3] m.p. °C
Me	H or Me	$C_3H_5N_3S_2$	58	240	240	—	—	—	—
Et	H or Et	$C_4H_7N_3S_2$	56	165	171	—	—	—	—
n-Pr	H or *n*-Pr	—				$C_5H_9N_3S_2$	54	156	—
n-Bu	H or *n*-Bu	—				$C_6H_{11}N_3S_2$	57	138	—
Me	Ph	$C_3H_5N_3S_2$	30	240	240	$C_8H_7N_3S_2$	38	228	219
"	*p*-MeC_6H_4	"	32	"	"	$C_9H_9N_3S_2$	44	222	216
"	*p*-ClC_6H_4	"	31	"	"	$C_8H_6ClN_3S_2$	36	200	—
"	*p*-$MeOC_6H_4$	"	30	"	"	$C_9H_9N_3OS_2$	40	228	—
"	*p*-$EtOC_6H_4$	"	32	"	"	$C_{10}H_{11}N_3OS_2$	41	205	—
Et	Ph	$C_4H_7N_3S_2$	33	165	171	$C_8H_7N_3S_2$	38	228	219
"	*p*-MeC_6H_4	"	31	"	"	$C_9H_9N_3S_2$	44	222	216
"	*p*-ClC_6H_4	"	33	"	"	$C_8H_6ClN_3S_2$	36	200	—
"	*p*-$MeOC_6H_4$	"	34	"	"	$C_9H_9N_3OS_2$	40	228	—
"	*p*-$EtOC_6H_4$	"	32	"	"	$C_{10}H_{11}N_3OS_2$	41	205	—
n-Pr/*n*-Bu	Ph	—				$C_8H_7N_3S_2$	73	228	219
"	*p*-MeC_6H_4	—				$C_9H_9N_3S_2$	74	222	216
"	*p*-ClC_6H_4	—				$C_8H_6ClN_3S_2$	69	200	—
"	*p*-$MeOC_6H_4$	—				$C_9H_9N_3OS_2$	71	228	—
"	*p*-$EtOC_6H_4$	—				$C_{10}H_{11}N_3OS_2$	72	205	—

*3,5-Bis(benzylthio)-4-methyl-1,2,4-triazole, m.p. 115°.
3,5-Bis(benzylthio)-4-ethyl-1,2,4-triazole hydrochloride, m.p. 133°.
5-Benzylthio-2-*n*-propylamino-1,3,4-thiadiazole, m.p. 156°.
5-Benzylthio-2-*n*-butylamino-1,3,4-thiadiazole, m.p. 138°.
5-Benzylthio-2-phenylamino-1,3,4-thiadiazole, m.p. 145°.

Other 1-alkyl-6-aryl-2,5-dithiobiureas were similarly cyclized, the products formed and their characterization data are given in Table 1.

Reaction of 4-methyl-1,2,4-triazolidine-3,5-dithione with benzyl chloride. Formation of 3,5-bis(benzylthio)-4-methyl-1,2,4-triazole

A solution of 4-methyl-1,2,4-triazolidine-3,5-dithione (3 g, 0.02 mmole) in alc sodium hydroxide (10%, 20 ml) was stirred with benzyl chloride (5.2 g, 0.04 mole) for 30 min when a white solid separated out. It was collected, washed with water and crystallized from ethanol to give 2,5-bis(benzylthio)-4-methyl-1,2,4-triazole as shining plates like crystals, m.p. 115° (yield 5.6 g, 75%).

Reaction of 2-phenylamino-Δ^2-1,3,4-thiadiazoline-5-thione with benzyl chloride. Formation of 5-benzylthio-2-phenylamino-1,3,4-thiadiazole

A solution of 2-phenylamino-Δ^2-1,3,4-thiadiazoline-5-thione (2.1 g, 0.01 mole) in aq sodium hydroxide (10%, 10 ml) was stirred with benzyl chloride (1.26 g, 0.01 mole) for 30 min. During this time a white solid product was separated out which was collected washed free of alkali and crystallized from ethanol as white needles shaped crystals of 5-benzylthio-2-phenylamino-1,3,4-thiadiazole (yield 2.4 g, 72%), m.p. 145°.

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Studies in spiroheterocycles: Part XI – Synthesis of novel fluorine containing 4′,5′-dihydrospiro[3*H*-indole-3,2′(1′*H*)-pyrazolo-[3,2-*d*][1,3,5]thiadiazepine]-2(1*H*),5′-diones from isatins

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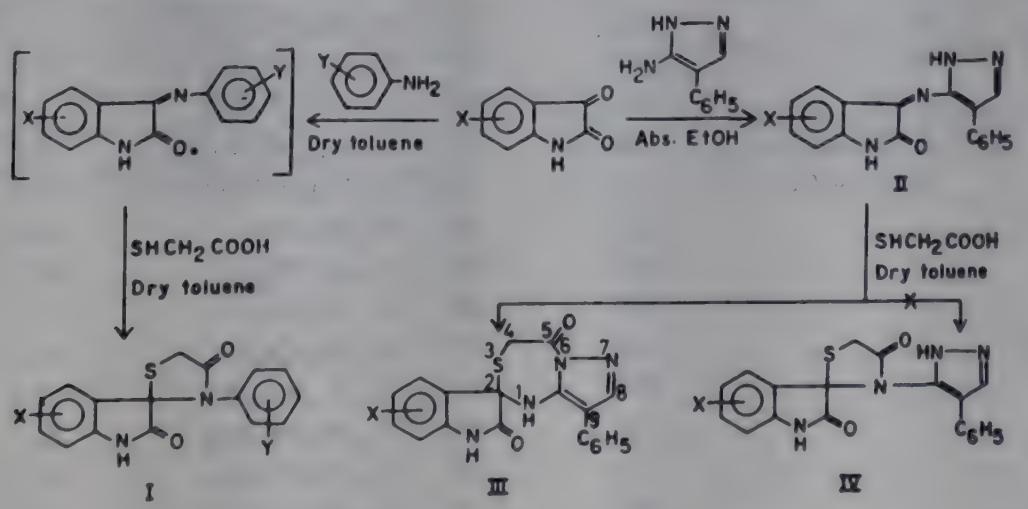
Reaction of mercaptoacetic acid with fluorinated 3-aryliminoindol-2-ones, prepared *in situ* from fluorinated indole-2,3-diones(isatins) and fluorinated anilines, yields 3′-arylspiro[3*H*-indole-3,2′-thiazolidine]-2(1*H*),4′-diones(I). Under similar conditions, 3-(4-phenylpyrazol-5-ylimino)indol-2-ones(II) yield a novel system 4′,5′-dihydro-9′-phenylspiro[3*H*-indole-3,2′(1′*H*)-pyrazolo[3,2-*d*][1,3,5] thiadiazepine]-2(1*H*),5′-dione (III). 3-(4-Phenylpyrazol-5-ylimino)indol-2-ones have been synthesized by the reaction of fluorine containing indole-2,3-diones with 3-amino-4-phenylpyrazole in abs. ethanol. The structures of the compounds have been established on the basis of elemental analyses, and IR, PMR, ^{19}F NMR and mass spectral data.

In continuation of our earlier work on the synthesis of fluorine containing indole derivatives for possible pharmacological evaluation, a series of new fluorine containing spiro[3*H*-indole-3,2′-thiazolidine]-2(1*H*), 4′-diones(I), 3-(4-phenylpyrazol-5-ylimino)indol-2-ones(II) and a novel spiro heterocyclic system 4′,5′-dihydro-9′-phenylspiro[3*H*-indole-3,2′(1′*H*)pyrazolo[3,2-d][1,3,5] thiadiazepine]-2(1*H*), 5′-diones(III) have been synthesized and screened for their herbicidal activity. Spiro compounds I were prepared because of the fact that spiro[indole-thiazolidines] have been found to be associated with a wide variety of biological activities[1-5].

The fluorinated spiro[3*H*-indole-3,2′-thiazolidine]-2(1*H*),4′-diones(I) were obtained by the reaction of mercaptoacetic acid with 3-aryliminoindol-2-ones, which in turn were prepared *in situ*, by condensation of isatin with aromatic amines. A slight excess of mercaptoacetic acid is found to give better yields[6] (75-80%). Further, the analogous reaction of 3-(4-phenylpyrazol-5-ylimino) indol-2-one(II) with mercaptoacetic acid was also investigated for the first time. This reaction appeared to be of interest as there are two possible reaction sites in this compound: (i) carboxyl group of mercaptoacetic acid may attack the imino nitrogen atom thereby forming a thiazolidine ring at C-3 of the indole nucleus to give compound IV (analogous to the formation of I), or (ii) carboxyl group may attack NH of the pyrazole ring affording a thiadizepine ring system at C-3 of the indole nucleus leading to the new heterocyclic system III.

Since NH of pyrazole ring seems to be more basic as compared to imino nitrogen, the attack of



carbonyl group is likely to be more favourable at NH of the pyrazole ring giving rise to a thiadiazepine ring system which indeed seems to be the case and has been confirmed by spectral studies. This is the first report on the synthesis of a spiro system incorporating indole and pyrazolothiadiazepine nuclei.

The spiro compounds I (Table 1) were characterized by the IR absorption bands at 1670 and 1730 due to νC=O and at 3200-3300 cm^{-1} for N-H stretching. The PMR signal due to methylene protons of the thiazolidine ring appeared as a double doublet at δ 3.8-4.35. The signals due to aromatic protons and indole NH appeared at δ 6.7-7.5 and 10.8-10.95 respectively. The mass spectra further supported the formation of these compounds as the parent peaks corresponded to their molecular weights. The mass spectra also showed a strong peak due to an aryl cation.

Formation of 3-(4-phenylpyrazol-5-ylimino) indol-2-ones(II) was indicated by the disappearance of one CO frequency of the isatin moiety and free primary amino frequency of aminopyrazole in the IR specra. Also, in the PMR spectra signals due to NH_2 protons were lacking and characteristic signals were observed at δ 10.90 (indole NH), 8.34 (pyrazole NH) and 7.9 (pyrazole methine) in addition to that for aromatic protons.

The IR spectra of the products formed by the reaction of II and mercaptoacetic acid showed absorption bands at 1700 and 1680 (νC=O), 2800-2980 (ν-CH_2-) and 3090-3350 cm^{-1} (νNH stretching) indicating the transformation of II into a spiro system. In PMR spectra, the disappearance of NH signal of pyrazole ring at δ 8.34 and appearance of the signal at 10.6 due to thiadiazepine NH proton also indicated the formation of the spiro product III containing a thiadiazepine ring system, instead of formation of the spiro product IV containing a thiazolidine ring system. Other characteristic signals observesd in the PMR spectra were a double doublet at δ 3.95-4.16 (-CH_2-CO), a singlet at 7.9 (pyrazole HC=N), a singlet at 10.85 (indole NH) and a multiplet at 6.5-7.5 (aromatic protons). These data also indicated the formation of the spiro system III. Presence of NH protons was confirmed by deuteration. The mass spectra further supported the formation of III instead of IV. In the fragmentation pattern of 3′-phenyl-4-trifluoromethylspiro[3*H*-indole-3,2′-thiazolidine]-2(1H),4′-dione(Ia), a characteristic feature was the elimination of the phenyl ring with the appearance of an intense peak (90%) at m/z 77 due to phenyl cation ($C_6H_5^+$). In the case of IIIa the parent peak appeared at m/z 362 (100%) corresponding to the molecular weight, but the expected elimination of pyrazole ring (as in the case of IV) was not observed in the mass spectrum.

The presence and positions of fluorine atoms in the compounds I, II and III were confirmed by ^{19}F NMR specra. A single fluorine atom attached to indole ring at position 6 or 5 was observed as a doublet at δ −115.147 and −115.494 (J_{HF} = 25.5 Hz). The fluorine atoms of trifluoromethyl group of indole moiety (Ia, IId, IIId) and of aryl ring (Ic, Ie) appeared as singlets at −62.968 and −63.249, respectively.

Table 1—Characterization data of 3-(4-phenylpyrazol-5-ylimino)indol-2-ones(II) and spiro compounds I and III

Compd	X	Y	m.p. °C	Yield (%)	Mol. formula	N(%)*	
						Calc	Found
Ia	4-CF_3	H	275	78	$C_{17}H_{11}F_3N_2O_2S$	7.7	7.6
Ib	5-F	H	264	80	$C_{16}H_{11}FN_2O_2S$	8.9	8.8
Ic	H	3-CF_3	210	80	$C_{17}H_{11}F_3N_2O_2S$	7.7	7.6
Id	H	3-CF_3, 4-Cl	240	78	$C_{17}H_{10}ClF_3N_2O_2S$	7.0	7.1
Ie	5-F	3-CF_3, 4-Cl	220	70	$C_{17}H_9ClF_4N_2O_2S$	6.7	6.6
IIa	H	—	235	85	$C_{17}H_{12}N_4O$	19.4	19.4
IIb	5-F	—	260	80	$C_{17}H_{11}FN_4O$	18.3	18.2
IIc	6-F	—	257	85	$C_{17}H_{11}FN_4O$	18.3	18.2
IId	4-CF_3	—	240	75	$C_{18}H_{11}F_3N_4O$	15.8	15.6
IIIa	H	—	272	75	$C_{19}H_{14}N_4O_2S$	15.5	15.3
IIIb	5-F	—	250	85	$C_{19}H_{13}FN_4O_2S$	14.7	14.6
IIIc	6-F	—	270	80	$C_{19}H_{13}FN_4O_2S$	14.7	14.7
IIId	4-CF_3	—	280	70	$C_{20}H_{13}F_3N_4O_2S$	13.0	13.2

*Satisfactory C and H analyses were also obtained.

Experimental Procedure

All melting points are uncorrected. IR spectra were recorded in KBr on a Perkin-Elmer 577 spectrophotometer (ν_{max} in cm^{-1}). PMR spectra in DMSO-d_6 on a Jeol FX 90 Q spectrometer at 89.5 MHz using TMS as internal reference and ^{19}F NMR spectra in TFA on a Jeol FX 90 Q spectrometer at 84.25 MHz using hexafluorobenzene as internal standard (all chemical shifts in δ, ppm). Purity of the compounds was checked by TLC on silica gel plates and spots were located either by iodine vapours or UV lamp. 5-Fluoro, 6-fluoro- and 4-trifluoromethyl-indole-2,3-diones were prepared by the methods reported in literature[7-9].

4-Trifluoromethyl-3′-phenylspiro[3H-indole-3,2′-thiazolidine]-2(1H),4′-dione(Ia)

A mixture of 4-trifluoromethylindole-2,3-dione (0.01 mole) and aniline (0.01 mole) was refluxed in dry toluene for 2 hr using a Dean-Stark apparatus and theoretical amounts of water were removed azeotropically. After cooling to room temperature, mercaptoacetic acid (0.011 mole) was added and the mixture refluxed for 4-5 hr till the formation of water from the reaction ceased. On cooling, a white solid was obtained which was purified by recrystallization from ethanol, yield 2.85 g (78%), m.p. 275° (Found: N, 7.6; S, 8.6. $C_{17}H_{11}F_3N_2O_2S$ requires N, 7.7; S, 8.6%); IR 3300-3150 (broad N-H) 1730, 1680 (both C=O), 1100-1000 (C-F); PMR: 3.9-4.35 (dd, 2H, $-CH_2-$), 6.4-7.5 (m, 8H, aromatic protons) and 10.75 (br, NH); MS: m/z 364 (M^+, 57%), 336 ($M^+ - CO$, 50%), 77 ($C_6H_5^+$, 90%). All other compounds(Ib-e) were prepared in a similar manner.

3-(4-Phenylpyrazol-5-ylimino)indol-2-one(IIa)

An equimolar mixture of indole-2,3-dione(0.01 mole) and 3-amino-4-phenylpyrazole (0.01 mole) was refluxed in abs. ethanol (50 ml) for 4 hr, and cooled when orange flakes of the desired compound were obtained which were filtered and recrystallized from ethanol, yield 2.45 g (85%), single spot on TLC, m.p. 235° (Found: N, 19.4. $C_{17}H_{12}N_2O$ requires N, 19.4%); IR: 3000-3300 (broad, N-H), 1700 (C=O), 1610 (C=N); PMR: 7.9 (s, 1H, pyrazolyl CH), 6.8-7.6 (m, 9H, aromatic protons), 8.34 (s, 1H, pyrazoly NH), 10.91 (s, 1H, indole NH). All other compounds (IIb-d) were prepared in a similar manner.

4′,5′-Dihydro-9′-phenylspiro[3H-indole-3,2′(1′H)-pyrazolo[3,2-d][1,3,5]thiadiazepine]-2(1H),5′-dione(IIIa)

A mixture of 3-(4-phenylpyrazol-5-ylimino)indol-2-one (0.01 mole) and mercaptoacetic acid (0.01 mole) was refluxed in dry toluene (50 ml) for 4 hr using a Dean-Stark apparatus and the waer formed removed azeotropically. On cooling, cream coloured crystals were obtained, which were recrystallized from ethanol, yield 2.7 g (75%), m.p. 272° (Found: N, 15.3; S, 8.8. $C_{19}H_{14}N_4O_2S$ requires N, 15.5; S, 8.8%); IR: 3400-3200 (both N-H), 1700, 1680 (both C=O), 2980-2800 (CH_2), 1600 (C=N); PMR: 3.95-4.16 (dd, 2H, CH_2), 6.7-7.5 (m, 9H, aromatic protons), 7.9 (s, HC=N), 10.6 (s, 1H, thiadiazepine NH), 10.9 (s, 1H, indole NH); MS: m/z 362 (M^+, 100%). All other compounds (IIIb-d) were prepared in a similar manner.

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Interaction of heterothiocumulenes with 2-amino-3-cyanothiophenes: Formation of thieno[2,3-*d*]pyrimidines

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Thieno-fused(1,3)-thiazine, 4-imino-2-thioxo-2,4-dihydro-1*H*-thieno[2,3-*d*](1,3)-thiazine (**2**) has been directly synthesised by the reaction of *o*-aminonitrile (**1a**) with carbon disulphide. Thiazine (**2**) on reaction with primary aromatic amines leads to thieno[2,3-*d*]pyrimidines (**3**). As a second approach the 2-bis(methylthio) methyleneamino-3-cyanothiophene (**4**) reacts with amines leading to the methylthio derivatives (**5**) of thieno[2,3-*d*]pyrimidines. Apart from the above two methods, thieno[2,3-*d*]pyrimidines are formed from the reaction of *o*-aminonitriles (**1a-c**) with isothiocyanates. The relative merits of the three methods are assessed.

Studies on the reaction of heterothiocumulenes with heterocyclic *o*-aminonitriles are very few[1-4], and fused 1,3-thiazines and pyrimidines have been reported as products under mild conditions favouring the former type of products. The title investigation form a part of our programme[5] concerning the synthesis of hetero-fused pyrimidine derivatives. Thieno fused 1,3-thiazines appear to have been reported only very rarely and the various synthesis[6-8] of this ring system reported involve the reaction of 2-aminothiophene-3-carboxamides with dithietane derivatives and of thienooxazines or 2-aminothiophene-3-carbethoxy esters with phosphorus pentasulphide.

Thiophene (**1a**) reacted with carbon disulphide in pyridine at room temperature to afford 4-imino-2-thioxo-2,4-dihydro-1*H*-thieno[2,3-*d*](1,3)-thiazine (**2**). When **2** was refluxed in ethanol in the presence of a base, it rearranged to the known 2,4-dithioxo-2,4-dihydro-1*H*,3*H*-thieno[2,3-*d*]pyrimidine[9]. Thiazine derivatives have been known to react with primary amines to afford pyrimidines, however there seems to be only one example of this approach to synthesize hetero-fused pyrimidines[4]. Interaction of primary alkylamines with **2** resulted only in the isomerisation of **2** to give the same 2,4-dithioxothieno[2,3-*d*]pyrimidine obtained by the base-catalysed rearrangement of **2** as mentioned above. Primary arylamines reacted with **2** at room temperature or upon heating to give 3-aryl-4-imino-2-thioxo-2,4-dihydro-1*H*,3*H*-thieno[2,3-*d*]pyrimidines (**3a-d**) (Scheme 1). Methylation of **2** with methyl iodide in the presence of a base resulted in the thiazine ring opening and gave the 2-[bis(methylthio)methyleneamino]-3-cyanothiophene (**4**). It appeared that **4** on reaction with amines could also lead to thieno[2,3-*d*]pyrimidines. However primary aryl or alkylamines did not react with **4** under a variety of conditions. Arylamine hydrochlorides when heated with **4** in the presence of hydrochloric acid afforded 3-aryl-4-imino-2-methylthio-3,4-dihydrothieno[2,3-*d*]pyrimidines (**5a-d**). These were found to be identical to the products obtained by the reaction of **3a-d** with methyl iodide.

To explore the general applicability of these routes to thieno-pyrimidines, 2-amino-3-cyanothiophenes (**1b,c**) were reacted with carbon disulphide. The thiophenes (**1b,c**) were found to be unreactive when treated with carbon disulphide in pyridine at room temperature. But at higher temperature related 2,4-dithioxothieno[2,3-*d*]pyrimidines (**2b**) and (**2c**) were formed in quantitative yields. The restrictive nature and lack of generality in the above routes to thieno[2,3-*d*]pyrimidines from the thiophene *o*-aminonitriles prompted us to explore their reaction with isothiocyanates.

The thiophene (**1a**) failed to react with the alkyl isothiocyanates at room temperature in DMF or pyridine. However stirring the reactants in DMF in the presence of powdered sodium hydroxide led to 3-alkyl-4-imino-2-thioxo-2,4-dihydro-1*H*,3*H*-thieno[2,3-*d*]pyrimidines (**3e-h**). This reaction condition was then found to be a very general one and the thiophene deri-

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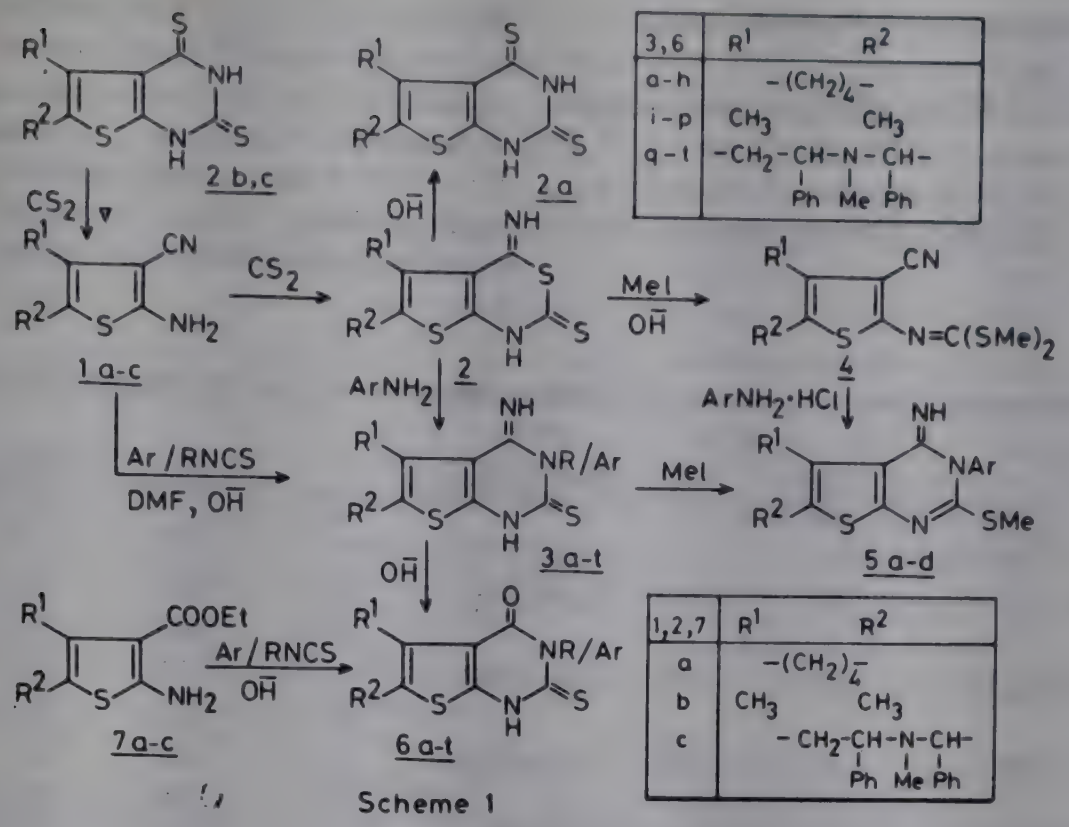

Scheme 1

vatives[10,11] **1a-c** reacted smoothly with alkyl and arylisothiocyanates to afford the thieno[2,3- *d*]pyrimidines (**3a-t**). The structure identification of these 4-iminothieno[2,3-*d*]pyrimidines was based on their hydrolysis to 4-oxothieno[2,3-*d*]pyrimidines (**6a-t**), a few of which were prepared unambiguously[10,12] for comparison purposes from 2-aminothiophene-3-carboxylates (**7a-c**) and isothiocyanates. The reaction of isothiocyanates with heterocyclic *o*-aminonitriles took lesser reaction time, did not induce a Dimroth rearrangement of the products and gave excellent yields as compared to the reported methods[1-3]. In addition, 4-oxo derivatives could also be obtained from 2-aminothiophene-3-carboxylate in one step. Such compounds were obtained earlier by a two step procedures[12-14].

Experimental Procedure

Melting points were taken in open capillaries and are uncorrected. PMR spectra were recorded on a Varian EM-360 (60 MHz) instrument, chemical shifts are reported in δ-scale downfield from TMS internal standard. IR spectra were taken in KBr on a Perkin-Elmer 397 spectrophotometer (ν_{max} in cm^{-1}) and mass spectra on a VG Micromass 70-70H spectrometer.

4-*Imino*-2-*thioxo*-2,4-*dihydro*-1*H*-*thieno*[2,3-*d*]-(1,3)-*thiazine* (**2**)

A solution of **1a** (2.5 g, 14 mmole) in a mixture of carbon disulphide (15 ml) and pyridine (10 ml) was kept for 24 hr at room temperature. After dilution with ether (100 ml), the precipitated product was collected, washed with ether and crystallised from methanol/dimethylformamide (2:1) to give **2**, yield 3.29 g (92%), m.p. 271° (Found: C, 47.3; H, 4.0; N, 11.1; S, 37.8. $C_{10}H_{10}N_2S_3$ requires C, 47.2; H, 4.0; N, 11.0; S, 37.8%); IR(KBr): 3380 (=NH), 3200 (thiazine NH), 3050, 1610; PMR(DMSO-d_6): 1.7 (4H, m, CH_2 at 5 and 6), 2.6 (4H, m, CH_2 at 6 and 7); MS: m/z 254 (M^+).

Compound **2** (50.9 g, 20 mmole) was refluxed in ethanol-water (5:1, 12 ml) containing sodium hydroxide (0.8 g) for 6 hr. The reaction mixture was poured into glacial acetic acid/water (1:1, 20 ml). The crude 2,4-dithioxo-2,4-dihydro-1H,3H-thieno[2,3-*d*]-pyrimidine was collected, washed with water and crystallized from 1-butanol; yield 4.89 g (96%), m.p. 250° (lit.[12], m.p. 250°) (Found: C, 47.2; H, 4.0; N, 11.1; S, 37.7. $C_{10}H_{10}N_2S_3$ requires C, 47.2; H, 4.0; N, 11.0; S, 37.8%); IR(KBr): 3200 (pyrimidine NH), 1560, 1540, 1490; PMR(DMSO-d_6): 1.67 (4H, m, CH_2 at 5 and 8), 2.57 (4H, m, CH_2 at 6 and 7); MS: m/z 254 (M^+).

2,4-*Dithioxo*-2,4-*dihydro*-1*H*,3*H*-5,6-*dimethyl*-*thieno*[2,3-*d*]*pyrimidine* (**2b**)

A solution of **1b** (2.1 g, 14 mmole) in a mixture of carbon disulphide (15 ml) and pyridine (10 ml) was heated at 80°, in a sealed tube for 2 hr. The reaction mixture was poured in to ether (100 ml), precipitated product collected, washed with ether and crystallised from 1-butanol to give **2b**; yield = 2.9 g (92%); m.p. 260° (Found: C, 42.0; H, 3.4; N, 12.0; S, 42.0. $C_8H_8N_2S_3$ requires C, 42.1; H, 3.5; N, 12.3; S, 42.1%); IR(KBr): 3200 (pyrimidine NH), 1550, 1530, 1490; PMR (DMSO-d_6): 2.50 (3H, s, CH_3 at 5), 2.90 (3H, s, CH_3 at 6); MS: m/z 228 (M^+).

2,4-Dithioxo-2,4-dihydro-1H,3H-pyridothieno-(2,3-d)pyrimidine (**2c**)

It obtained from **1c** following the procedure adopted for **2b**; yield 87%; m.p. 348° (Found: C, 68.0; H, 5.2; N, 11.0; S, 16.8. $C_{22}H_{19}N_3S_2$ requires C, 67.9; H, 4.9; N, 10.8; S, 16.5%); IR(KBr): 3200 (pyrimidine NH); 1560, 1540, 1500.

Reaction of **2** *with primary arylamines: 3-Aryl-4-imino-2-thioxo-2,4-dihydro-1H,3H-thieno[2,3-d]-pyrimidines* (**3a-d**): *General procedure*

A mixture of arylamine (30 mmole) and compound **2** (0.509 g, 2 mmole) was kept at 80°C for 1 hr and diluted with ether (50 ml). The solid obtained was collected and crystallized from Jimethylformamide/eth-

Table 1 – Characterisation data of various 3-alkyl or aryl-4-imino-2-thioxo 2,4-dihydro-1H,3H-thieno[2,3-*d*]pyrimidines (**3**) prepared

Compd	R/Ar	Yield (%)	m.p. °C	Mol. formula	Found (%) (Calc.)			
					C	H	N	S
3a	C_6H_5	93	253	$C_{16}H_{15}N_3S_2$	61.4	4.9	13.5	20.6
					(61.3)	(4.8)	(13.4)	(20.5)
3b	4-$H_3C-C_6H_4$	92	255	$C_{17}H_{17}N_3S_2$	62.5	5.3	13.0	19.7
					(62.3)	(5.3)	(12.9)	(19.6)
3c	4-$Cl-C_6H_4$	93	260	$C_{16}H_{14}ClN_3S_2$	55.3	4.1	12.1	18.4
					(55.1)	(4.0)	(12.0)	(18.3)
3d	4-$H_3CO-C_6H_4$	92	290	$C_{17}H_{17}N_3OS_2$	59.4	5.0	12.2	18.9
					(59.5)	(5.1)	(12.3)	(18.7)
3e	CH_3	90	256	$C_{11}H_{13}N_3S_2$	52.5	5.4	16.8	25.6
					(52.6)	(5.3)	(16.7)	(25.5)
3f	C_2H_5	87	251	$C_{12}H_{15}N_3S_2$	54.3	5.9	15.9	24.3
					(54.3)	(5.7)	(15.9)	(24.3)
3g	C_3H_7	85	248	$C_{13}H_{17}N_3S_2$	56.0	6.3	15.1	23.1
					(55.9)	(6.2)	(15.0)	(23.0)
3h	C_4H_9	85	241	$C_{14}H_{19}N_3S_2$	57.4	6.6	14.4	22.0
					(57.3)	(6.5)	(14.3)	(21.9)
3i	C_6H_5	85	239	$C_{14}H_{13}N_3S_2$	58.6	4.6	14.7	22.4
					(58.5)	(4.6)	(14.6)	(22.3)
3j	4-$H_3C-C_6H_4$	82	234	$C_{15}H_{15}N_3S_2$	60.0	5.2	14.0	21.4
					(59.8)	(5.1)	(13.9)	(21.3)
3k	4-$Cl-C_6H_4$	85	240	$C_{14}H_{12}ClN_3S_2$	52.5	3.9	13.1	19.9
					(52.4)	(3.8)	(13.1)	(19.9)
3l	4-$H_3CO-C_6H_4$	83	230	$C_{15}H_{15}N_3OS_2$	57.0	4.9	13.3	20.2
					(56.8)	(4.8)	(13.2)	(20.3)
3m	CH_3	80	228	$C_9H_{11}N_3S_2$	48.2	5.0	18.7	28.6
					(48.0)	(4.9)	(18.7)	(28.5)
3n	C_2H_5	81	227	$C_{10}H_{13}N_3S_2$	50.4	5.6	17.6	26.9
					(50.2)	(5.5)	(17.6)	(26.8)
3o	C_3H_7	80	221	$C_{11}H_{15}N_3S_2$	52.4	6.1	16.7	25.5
					(52.1)	(6.0)	(16.6)	(25.3)
3p	C_4H_9	80	218	$C_{12}H_{17}N_3S_2$	54.0	6.4	15.7	24.1
					(53.9)	(6.4)	(15.7)	(23.9)
3q	C_6H_5	81	272	$C_{28}H_{24}N_4S_2$	70.1	5.2	11.8	13.5
					(70.0)	(5.1)	(11.7)	(13.4)
3r	4-$H_3C-C_6H_5$	80	268	$C_{29}H_{26}N_4S_2$	70.6	5.5	11.4	13.1
					(70.4)	(5.3)	(11.3)	(13.0)
3s	CH_3	81	282	$C_{23}H_{22}N_4S_2$	66.1	5.4	13.6	15.5
					(66.0)	(5.3)	(13.4)	(15.3)
3t	C_2H_5	80	278	$C_{24}H_{24}N_4S_2$	67.3	5.8	13.2	14.9
					(67.2)	(5.6)	(13.0)	(14.8)

Table 2 – Characterisation data of various 3-aryl-4-imino-2-methylthio-3,4-dihydrothieno[2,3-*d*]pyrimidines (**5**)

Compd	R/Ar	Yield (%)	m.p. °C	Mol. formula	Found (%) (Calc.)			
					C	H	N	S
5a	C_6H_5	60	243	$C_{17}H_{17}N_3S_2$	62.7 (62.5)	5.3 (5.2)	12.9 (12.8)	19.6 (19.5)
5b	4-$H_3C-C_6H_4$	60	235	$C_{18}H_{19}N_3S_2$	63.6 (63.5)	5.7 (5.6)	12.2 (12.2)	18.8 (18.7)
5c	4-$Cl-C_6H_4$	60	240	$C_{17}H_{16}ClN_3S_2$	56.8 (56.6)	4.5 (4.4)	11.5 (11.6)	17.7 (17.6)
5d	4-$H_3CO-C_6H_4$	58	235	$C_{18}H_{19}N_3OS_2$	60.9 (60.7)	5.4 (5.3)	11.8 (11.7)	17.9 (17.9)

Table 3 – Characterisation data of various 3-alkyl or aryl-4-oxothieno[2,3-*d*]pyrimidines (**6**)

Compd	R/Ar	Yield (%)	m.p. °C (lit)	Mol. formula (lit)	Found (%) (Calc.)			
					C	H	N	S
6a	C_6H_5	90	315 (315)					
6b	4-$H_3C-C_6H_4$	89	289 (280-83)					
6c	4-$Cl-C_6H_4$	90	263	$C_{16}H_{13}ClN_2OS_2$	55.0 (55.1)	3.7 (3.8)	7.8 (8.0)	18.3 (18.4)
6d	4-$H_3CO-C_6H_4$	90	292	$C_{17}H_{16}N_2O_2S_2$	59.1 (59.3)	4.5 (4.7)	8.1 (8.1)	18.4 (18.6)
6e	CH_3	83	301 (298-301)					
6f	C_2H_5	88	261 (259-61)					
6g	C_3H_7	83	247	$C_{13}H_{16}N_2OS_2$	55.4 (55.7)	5.6 (5.8)	9.8 (10.0)	22.5 (22.9)
6h	C_4H_9	83	234	$C_{14}H_{18}N_2OS_2$	57.0 (57.1)	6.0 (6.2)	9.3 (9.5)	21.5 (21.8)
6i	C_6H_5	83	310 (308-10)					
6j	4-$H_3C-C_6H_4$	83	221 (220)					
6k	4-$Cl-C_6H_4$	83	242	$C_{14}H_{11}N_2OS_2Cl$	52.0 (52.1)	3.2 (3.4)	8.4 (8.7)	19.7 (19.9)
6l	4-$H_3CO-C_6H_4$	78	253	$C_{15}H_{14}N_2O_2S_2$	56.4 (56.6)	4.2 (4.4)	8.5 (8.8)	19.8 (20.1)
6m	CH_3	83	273 (270-74)					
6n	C_2H_5	80	258 (255-57)					
6o	C_3H_7	79	243	$C_{11}H_{14}N_2OS_2$	52.0 (52.0)	5.7 (5.6)	11.1 (11.0)	25.3 (25.2)
6p	C_4H_9	80	237	$C_{12}H_{16}N_2OS_2$	53.8 (53.7)	6.1 (6.0)	10.5 (10.4)	24.0 (23.9)
6q	C_6H_5	85	321	$C_{28}H_{23}N_3OS_2$	69.8 (70.0)	5.0 (4.8)	8.8 (8.7)	13.5 (13.3)
6r	4-$H_3C-C_6H_4$	83	315	$C_{29}H_{25}N_3OS_2$	70.4 (70.3)	5.3 (5.1)	8.7 (8.5)	13.1 (13.0)
6s	CH_3	78	292	$C_{23}H_{21}N_3OS_2$	65.3 (65.5)	4.8 (5.1)	9.7 (10.0)	15.0 (15.3)
6t	C_2H_5	76	289	$C_{24}H_{23}N_3OS_2$	66.3 (66.5)	5.1 (5.4)	9.3 (9.7)	14.5 (14.7)

anol (Table 1). The product **3a** was also obtained in comparable yield by keeping **2** dissolved in aniline for 20 hr at room temperature followed by dilution with ether.

3-Alkyl or aryl-4-imino-2-thioxo-2,4-dihydro-1H,3H-thieno[2,3-d] pyrimidines (**3a-t**): *General procedure*

Alkyl or aryl isothiocyanate (10 mmole) was added dropwise to a stirred mixture of **1a-c** (10 mmole) and powdered sodium hydroxide (0.4 g, 10 mmole) in dimethylformamide (10 ml). After stirring for 1 hr, the reaction mixture was poured into dilute acetic acid (5%, 100 ml). The precipitated product was collected and crystallised from dimethylformamide/ethanol (Table 1).

2-[Bis(methylthio)methyleneamino]-3-cyanothiophene (**4**)

To a stirred solution of **2** (0.509 g, 2 mmole) in 1 *N* aq. potassium hydroxide (20 ml), methyl iodide (2 g) was added. After 1 hr, the precipitated product **4** was collected and crystallised from methanol; yield 0.51 g (90%), m.p. 118° (Found: C, 51.1; H, 5.1; N, 10.0; S, 34.1. $C_{12}H_{14}N_2S_3$ requires C, 51.0; H, 5.0; N, 9.9; S, 34.1%); IR(KBr); 2200 (C≡N), 1530, 1420, 920; PMR(DMSO-d_6): 1.8 (4H, m, CH_2 at 4 and 7), 2.6 (6H, s, 2 MeS), 2.8 (4H, m, CH_2 at 5 and 6); MS: m/z 282 (M^+).

3-Aryl-4-imino-2-methylthio-3,4-dihydrothieno-[2,3-d]pyrimidines (**5a-d**): *General procedure*

A mixture of **4** (0.564 g, 2 mmole) and arylamine hydrochloride (5 mmole) was made into a paste with 2-3 drops of conc hydrochloric acid and heated at 60-70° for 10 min. The mixture was dissolved in water (20 ml) and the solution neutralized by addition of solid sodium bicarbonate. The solid so obtained was collected and crystallised from methanol (Table 2). These compound (**5a-d**) were also obtained by adding methyl iodide (5 mmole) to a stirred solution of **3a-d** (2 mmole) in ethanol (10 ml) containing sodium hydroxide (0.2 g, 5 mmole). The precipitated product was collected and crystallised as above (Table 2).

4-Oxothieno[2,3-d]pyrimidines (**6a-t**): *General procedure*

Alkyl or aryl isothiocyanate (10 mmole) was added dropwise to a stirred mixture of **7a-c** (10 mmole) and powdered sodium hydroxide (0.4 g, 10 mmole) in dimethylformamide (10 ml). After stirring for 1 hr, the reaction mixture was poured into dil acetic acid (5%, 5 ml). The precipitated product was collected and crystallised from dil acetic acid. These products (**6a-t**) were also obtained by refluxing **3a-t** (2 mmole) in an aq potassium hydroxide (1 *M*, 25 ml) for 2 hr and pouring the cooled solution into dilute acetic acid (1:1, 100 ml). The precipitated solid was collected and crystallised as above (Table 3).

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Synthesis and reactions of phthalazine derivatives: Part I – Acylation and condensation of 1(2*H*)-oxo-4-phenyl-phthalazine-2-acetic acid hydrazide: Synthesis of heterobicyclics and heterobicyclylmethanes

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Acylation and condensation of 1(2*H*)-oxo-4-phenylphthalazine-2-acetic acid hydrazide (Ic) with esters, acid halides, substituted thioisocyanates, acrylonitrile, aldehydes, oxoacids, ketones and 1,2- and 1,3-bicarbonyl compounds have been carried out to get heterobicyclic compounds and substituted heterocyclylmethanes. Their structures have been established on the basis of elemental analysis and spectral data.

A recent publication by Merchant *et al.*[1] prompted us to undertake the synthesis of some new heterocyclic systems and substituted heterobicyclylmethanes by the reaction of phthalazine derivatives with different substrates.

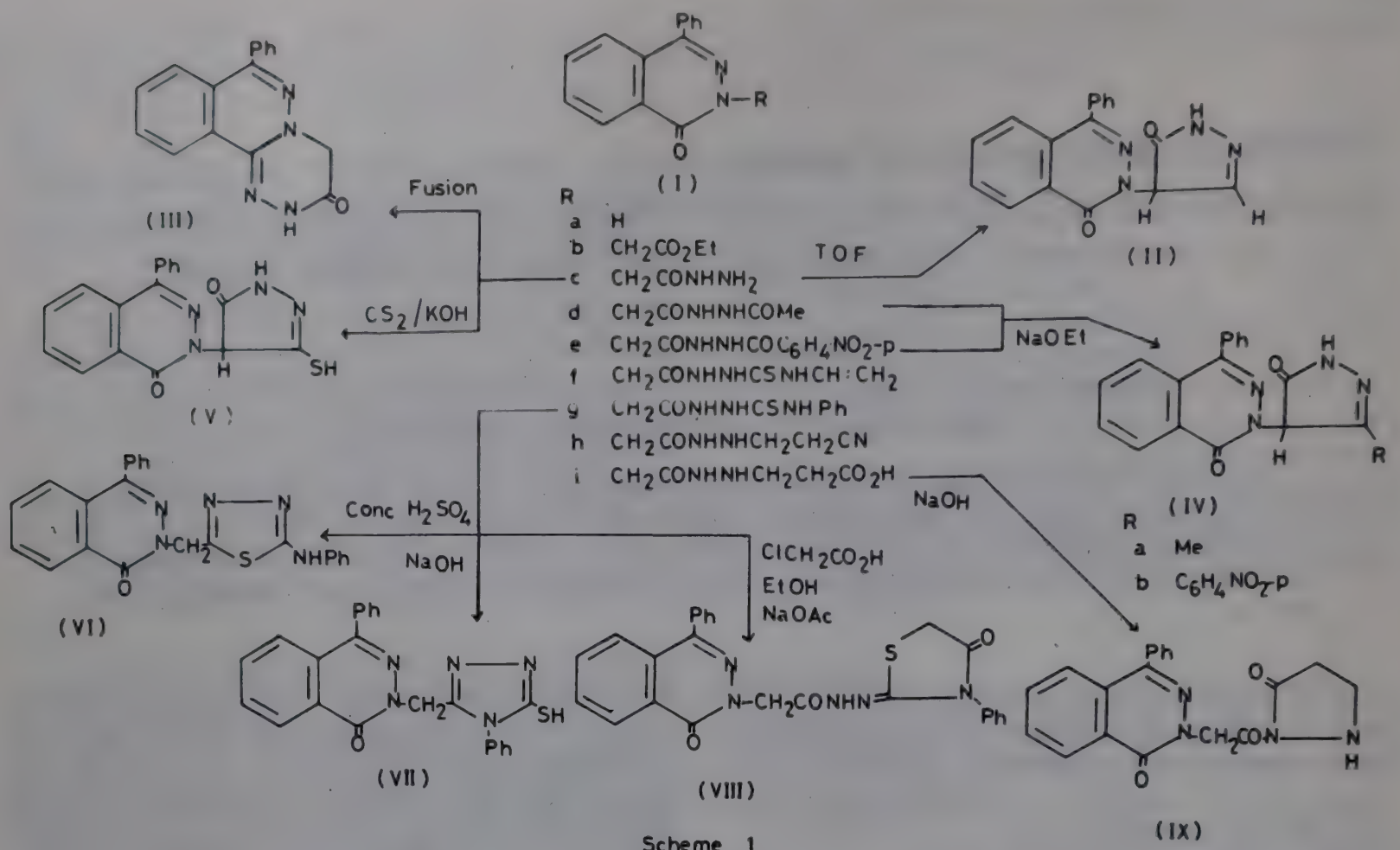
2-Benzoylbenzoic acid on condensation with hydrazine hydrate in abs. ethanol yielded 4-phenylphthalazin-1-one (Ia)[1], alkylation of which with ethyl bromoacetate[2] gave 1(2*H*)-oxo-4-phenylphthalazine-2-acetic acid ethyl ester (Ib) which underwent hydrazinolysis[3] to give the corresponding acetic acid hydrazide (Ic). Treatment of Ic with acetyl chloride, *p*-nitrobenzoyl chloride, allyl isothiocyanate, phenyl isothiocyanate and acrylonitrile[4] gave the corresponding 1,2-biacetylhydrazine (Id), 1-aroyl-2-acetylhydrazine (Ie), 1,4-disubstituted thiosemicarbazides If and Ig and 1-cyanoethyl-2-acetylhydrazine (Ih), respectively. Hydrolysis of Ih with dil HCl gave 2-acetylhydrazine-1-propionic acid derivative (Ii), while refluxing of Ic with triethyl orthoformate produced 3,4-dihydro-4-[1′(2′*H*)-oxo-4′-phenylphthalazin-2′-yl]pyrazol-3(1*H*)-one (II). However, fusion of Ic at 200° led[5] to the formation of 3,4-dihydro-7-phenyl[1,2,4]triazino[3,4-*a*]phthalazin-3-one (III) (Scheme 1).

On the other hand, refluxing of Id and Ie with sodium ethoxide afforded 5-substituted-3,4-dihydro-4-[1′(2′*H*)-oxo-4′-phenylphthalazin-2′-yl] pyrazol-3(1H)-ones (IVa,b), while boiling of Ic with carbon disulphide in the presence of potassium hydroxide and ethanol produced 3,4-dihydro-5-mercapto-4-[1′(2′*H*)-oxo-4′-phenylphthalazin-2′-yl]pyrazol-3(2*H*)-one (V). Cyclization of Ig using conc. H_2SO_4 directly led[6] to the formation of 2-anilino-5-[1′(2′*H*)-oxo-4′-phenylphthalazin-2′-ylmethyl]-1,3,4-thiadiazole (VI) while cyclization under basic condition using aq. NaOH afforded 2-mercapto-1-phenyl-5-[1′(2′*H*)-oxo-4′-phenylphthalazin-2′-ylmethyl)-1,3,4-triazole (VII). Moreover, refluxing of Ig with monochloroacetic acid in the presence of NaOAc – EtOH[7] gave 1(2*H*)-oxo-4-phenylphthalazine-2-acetic acid 4-oxo-3-phenyl-2-thiazolidinylidenehydrazide (VIII). Basic cyclization of Ii by refluxing with 2*N* NaOH gave 3-oxo-2-[1′(2′*H*)-oxo-4′-phenylphthalazin-2-ylmethylcarbonyl]pyrazolidine (IX; Scheme 1).

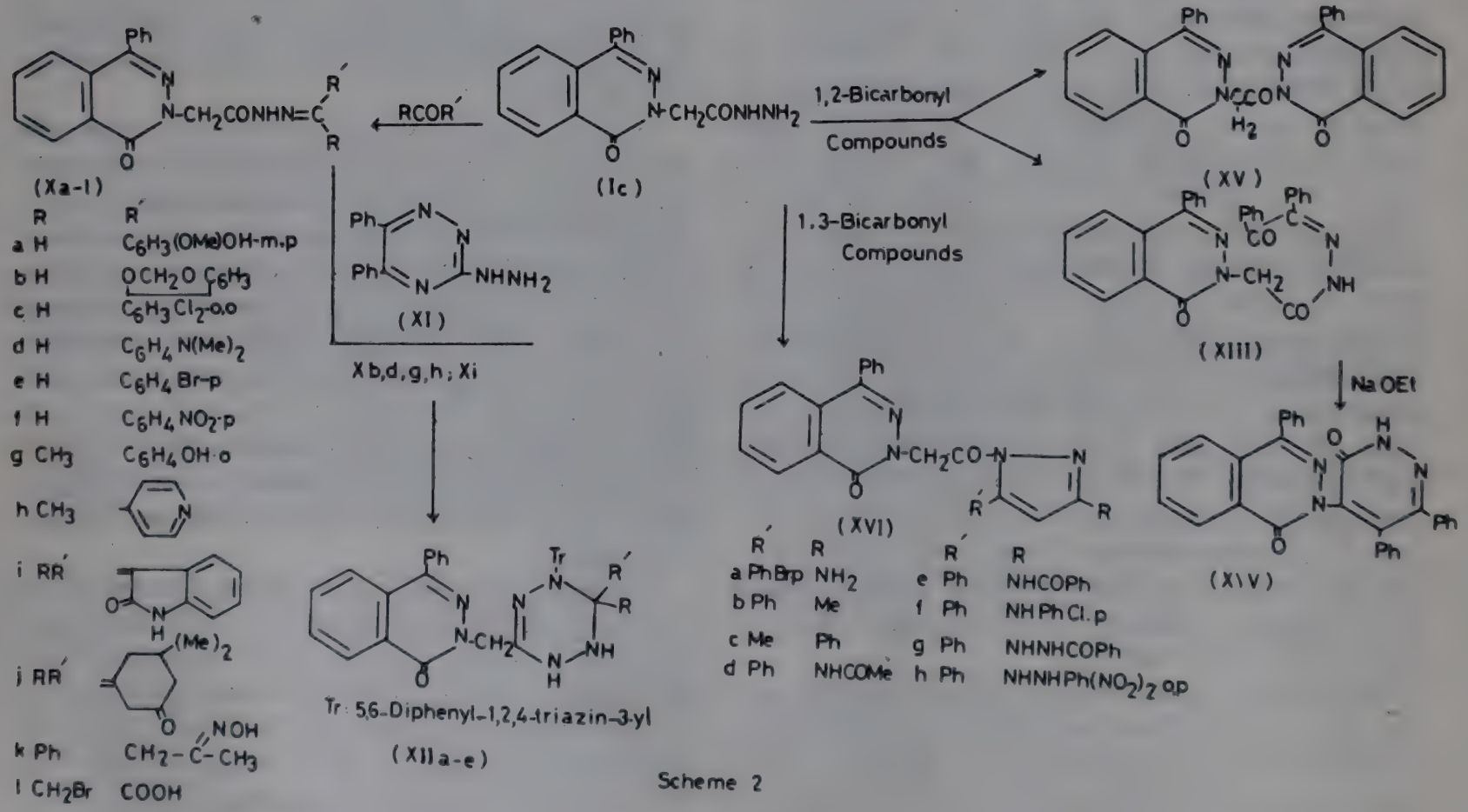
Reactions of Ic with various carbonyl compounds were also investigated. It underwent condensation with aldehydes, ketones, 1-benzoylacetone-2-oxime and β-bromopyruvic acid (an α-oxo acid) in ethanol containing a few drops of acetic acid to give the hydrazones (Xa-1), some (Xb,d,g,h,i) of which underwent cyclization when refluxed with 3-hydrazino-5,6-diphenyl-1,2,4-triazine (XI) in the presence of ethanol-piperdine[8] to give 6,6-disubstituted-1,2,5,6-tetrahydro-3-[1′(2′*H*)-oxo-4′-phenylphthalazin-2′-ylmethyl]-5-(5″,6″-diphenyl-1″,2″,4″-triazin-3″-yl)-1,2,4,5-tetrazines (XIIa-e) (Scheme 2).

Treatment of Ic with excess of benzil in abs. EtOH – gl.AcOH mixture produced the benzil monohydrazone (XIII) which underwent cyclization with sodium ethoxide to give 4-[1′(2′*H*)-oxo-4′-phenylphthalazin-2′-yl]-5,6-diphenylpyridiazin-3-(2*H*)-one (XIV). On the other hand, compound Ic when refluxed with 2-benzoylbenzoic acid in the presence of gl. acetic acid produced 1,2-bis[1′(2′*H*)-oxo-4′-phenylphthalazin-3′-yl]ethanone (XV; Scheme 2).

Moreover, reaction of Ic with unsymmetrical 1,3-dicarbonyl compounds such as α-cyanoacetophenone, benzoylacetone, benzoylacetone-1-hydrazone-2-oxime, N-acetylbenzoylacetamide, N-benzoylbenzoylacetamide, benzoylacetanilide, N^1-benzoyl-N^2-



Scheme 1



Scheme 2

benzoylacetylhydrazine and benzoylacetic acid hydrazide[8] in gl. acetic acid under reflux led directly to the formation of 3,5-disubstituted 1-[1′(2′*H*)-oxo-4′-phenylphthalazin-2′-ylmethylcarbonyl]pyrazoles (XVI a-i; Scheme 2).

Experimental Procedure

Melting points are uncorrected. Purity of the compounds was checked by paper chromatography using chloroform-ethyl acetate (9:1) as irrigant. IR spectra were recorded in KBr on a Perkin-Elmer 293 spectro-

photometer (ν_{max} in cm^{-1}) and PMR spectra in DMSO – d_6 on a Varian EM-390 90 MHz NMR spectrometer using TMS as internal standard (chemical shifts in δ, ppm). Compound Ia was prepared by the procedure followed by Merchant *et al.*[1]

1(2H)-Oxo-4-phenylphthalazine-2-acetic acid ethyl ester (Ib)

To a solution of sodium (0.01 mol) in abs. ethanol (100 ml) was added Ia (0.01 mol). The solution was stirred below 10° while ethyl bromoacetate (0.01 mol) added to it dropwise. When the addition was over, the reaction mixture was heated under reflux for 2 hr, cooled at room temperature and filtered to remove sodium bromide. The solid obtained upon dilution was filtered off to give Ib (Table 1).

1(2H)-Oxo-4-phenylphthalazine-2-acetic acid hydrazide (Ic)

A mixture of Ib (0.01 mol) and hydrazine hydrate (2 ml) in abs. ethanol (50 ml) was refluxed for 3 hr, and cooled at room temperature. The resultant solid was filtered to give Ic (Table 1); IR: 3300 (NH_2), 3150 (NH), 3020 (CH, aromatic), 2900 (C – H, aliphatic), 1700-1640 (2 C = O), 1480 (def. CH_2), 980, 900 (benzene ring).

Preparation of Id and Ie

A mixture of Ic (0.01 mol) and acetyl chloride or *p*-nitrobenzoyl chloride (0.01 mol) in the presence of DMF (50 ml) was heated under reflux for 4 hr, cooled, poured into cold water and the resultant solid filtered to give Id or Ie (Table 1).

Reaction of Ic with allyl isothiocyanate and phenyl isothiocyanate: Formation of If and Ig

A mixture of Ic (0.01 mol) and allyl isothiocyanate or phenyl isothiocyanate (0.01 mol) in pyridine-ethanol mixture (1:1, 100 ml) was heated under reflux for 2 hr, cooled, diluted with H_2O, acidified with HCl, and filtered to give If or Ig (Table 1); IR of Ig: 3300 (NH), 3220-3100 (– NH – NH –), 3020 (CH, aromatic), 2920 (CH, aliphatic), 1700-1670 (2 C = O), 1600 (C = N), 1480 (def. CH_2), 1350 (– NH, CSNH –), 1180 (C – S), 960, 920 and 800 (phenyl groups).

Preparation of Ih

A mixture of Ic (0.01 mol) and acrylonitrile (0.01 mol) in pyridine-water mixture (1:1, 20 ml) was heated under reflux for 4 hr, cooled, diluted with H_2O, acidified with HCl and filtered to give Ih (Table 1); IR: 3400 (NH), 3280 (NH), 3050 (CH aromatic), 2920 (CH, aliphatic), 2220 (C ≡ N), 1710-1640 (2 C = O), 1570 (C = N), 1430 (def. CH_2), 1000 and 800 (phenyl groups); PMR: 2.7 (2H, t, CH_2CN), 3.2 (2H, q, CH_2 – NH), 4.7 (2H, s, CH_2 – CO), 7.5 (5H, m, C_6H_5), 7.8 (4H, m, C_6H_4), 8.8 (1H, t, NH – CH_2) and 9.4 (1H, d, NHCO). The NH proton of acetic acid hydrazide derivative disappeared on shaking with D_2O.

Hydrolysis of Ih: Formation of Ii

A mixture of Ih (0.2 mol) and hydrochloric acid (200 ml) was refluxed for 2 hr, the reaction mixture cooled at room temperature and the solid obtained was filtered to give Ii (Table 1); IR: 3500-3400 (OH, NH), 3200-3100 (– NH –), 3020 (CH, aromatic), 2900 (CH, aliphatic), 1750-1690 (C = O, acid), 1670-1640 (2 C = O), 1470 (def. CH_2), 1000 and 850 (phenyl rings).

3,4-Dihydro-4-[1'(2'H)-oxo-4'-phenylphthalazin-2'-yl]pyrazol-3-(1H)-one] (II)

A mixture of Ic (0.01 mol) and triethyl orthoformate (10 ml) was heated under reflux for 4 hr on a steam-bath, cooled and diluted with water. The resultant solid was filtered to give II (Table 1).

3,4-Dihydro-7-phenyl[1,2,4]triazino[3,4-a]phthalazin-3-one (III)

Compound Ic was heated in an oil-bath at 200° for 1 hr, cooled the resultant solid recrystallized from an appropriate solvent to give III (Table 1); IR: 3200-3100 (– NH –), 3040 (CH, aromatic), 2940 (CH, aliphatic), 1670-1650 (C = O), 1610-1570 (C = N), 1480 (def. CH_2), 1000, 920, 800 (phenyl rings); PMR: 3.2 (2H, s, CH_2), 7.5 (5H, m, C_6H_5), 7.8 (4H, m, C_6H_4) and 10.1 (1H, s, NH exchangeable with D_2O).

Reaction of Id, Ie with sodium ethoxide: Formation of IVa,b

To a solution of sodium ethylate (prepared by dissolving 0.23 g. sodium in 20 ml abs. ethanol) was added to Id or Ie and the reaction mixture refluxed for 2 hr. The solid obtained upon dilution and acidification was filtered and recrystallized from an appropriate solvent to give IVa or IVb (Table 1).

3,4-Dihydro-5-mercapto-4-[1'(2'H)-oxo-4'-phenylphthalazin-2'-yl]pyrazol-3(1H)-one (V)

To a solution of potassium hydroxide in ethanol were added Ic (0.01 mol) and carbon disulphide (30 ml) and the reaction mixture was refluxed for 4 hr. The solid obtained upon dilution and acidification was filtered and recrystallized from an appropriate solvent to give V (Table 1); IR: 3200 (NH), 3020 (CH, aromatic), 2940 (CH, aliphatic), 2650 (SH), 1720 (C = O), 1660 (C = O), 1570 (C = N), 1480 (def. CH, aliphatic) and 940 (phenyl group).

Table 1 – Characterization data of the various compounds prepared

Compd	Crystallized from	m.p. °C	Yield (%)	Mol. formula	Found (%) (Calc.*)	
					N	S
Ib	EtOH	194	80	$C_{18}H_{16}N_2O_3$	8.5 (9.1)	—
Ic	EtOH	245	75	$C_{16}H_{14}N_4O_2$	18.8 (19.0)	—
Id	AcOH	195	70	$C_{18}H_{16}N_4O_3$	16.0 (16.7)	—
Ie	DMF	185	80	$C_{23}H_{17}N_5O_5$	15.0 (15.8)	—
If	EtOH	175	80	$C_{19}H_{17}N_5SO_2$	17.8 (18.5)	8.2 (8.4)
Ig	Pyridine	221	90	$C_{23}H_{19}N_5SO_2$	15.9 (16.3)	7.2 (7.5)
Ih	EtOH	165	60	$C_{19}H_{17}N_5O_2$	19.2 (20.2)	—
Ii	Benzene	110	60	$C_{19}H_{18}N_4O_4$	14.7 (15.3)	—
II	Triethyl orthoformate	230	70	$C_{17}H_{12}N_4O_2$	17.8 (18.4)	—
III	AcOH	295	75	$C_{16}H_{12}N_4O$	19.4 (20.3)	—
IVa	EtOH	230	60	$C_{18}H_{14}N_4O_2$	17.0 (17.6)	—
IVb	DMF	280	70	$C_{23}H_{15}N_5O_4$	15.9 (16.5)	—
V	EtOH	185	75	$C_{17}H_{12}N_4SO_2$	15.9 (16.7)	8.9 (9.5)
VI	DMF	235	60	$C_{23}H_{17}N_5SO$	16.2 (17.0)	7.8 (7.8)
VII	MeOH	295	65	$C_{23}H_{17}N_5SO$	16.4 (17.0)	7.7 (7.8)
VIII	DMF	230	80	$C_{25}H_{19}N_5SO_3$	14.1 (14.9)	6.2 (6.8)
IX	EtOH	187	60	$C_{19}H_{16}N_4O_3$	15.30 (16.1)	—
Xa	AcOH	240	80	$C_{24}H_{20}N_4O_4$	12.2 (13.1)	—
Xb	AcOH	266	85	$C_{24}H_{18}N_4O_4$	13.0 (13.1)	—
Xc	DMF	277	80	$C_{23}H_{16}N_4Cl_2O_2$†	11.9 (12.4)	—
Xd	DMF	285	80	$C_{25}H_{23}N_5O_2$	16.0 (16.5)	—
Xe	DMF	260	70	$C_{23}H_{17}N_4BrO_2$‡	12.0 (12.1)	—
Xf	DMF	276	70	$C_{23}H_{17}N_5O_4$	15.8 (16.4)	—
Xg	AcOH	238	80	$C_{24}H_{20}N_4O_3$	12.8 (13.6)	—

(contd.)

Table 1 – Characterization data of the various compounds prepared – Contd.

Compd	Crystallized from	m.p. °C	Yield (%)	Mol. formula	Found (%) (Calc.*)	
					N	S
Xh	DMF	275	80	$C_{23}H_{19}N_5O_2$	17.2 (17.6)	—
Xi	AcOH	237	85	$C_{25}H_{17}N_5O_3$	15.5 (16.5)	—
Xj	AcOH	290	70	$C_{22}H_{20}N_4O_3$	13.7 (14.4)	—
Xk	DMF	235	85	$C_{25}H_{21}N_5O_3$	15.1 (15.9)	—
XI	AcOH	290	80	$C_{19}H_{15}N_4BrO_4$§	12.0 (12.6)	—
XIIa	DMF	209	60	$C_{40}H_{29}N_9O_3$	17.9 (18.4)	—
XIIb	DMF	220	65	$C_{41}H_{34}N_{10}O$	19.9 (20.5)	—
XIIc	DMF	265	70	$C_{39}H_{31}N_9O_2$	18.7 (19.2)	—
XIId	DMF	225	60	$C_{38}H_{30}N_{10}O$	21.0 (21.8)	—
XIIe	DMF	175	60	$C_{40}H_{28}N_{10}O_2$	20.8 (21.1)	—
XIII	EtOH	210	80	$C_{30}H_{22}N_4O_3$	11.2 (11.5)	—
XIV	AcOH	265	70	$C_{30}H_{20}N_4O_2$	11.5 (12.0)	—
XV	EtOH	240	85	$C_{30}H_{20}N_4O_3$	11.0 (11.6)	—
XVIa	MeOH	135	70	$C_{25}H_{18}N_5BrO_2$**	13.1 (14.0)	—
XVIb	EtOH	175	75	$C_{26}H_{19}N_4O_2$	12.6 (13.7)	—
XVIc	AcOH	285	60	$C_{26}H_{19}N_4O_2$	13.0 (13.4)	—
XVId	dil. AcOH	210	80	$C_{27}H_{21}N_5O_2$	15.0 (15.7)	—
XVIe	Dioxane	295	70	$C_{32}H_{23}N_5O_3$	13.1 (13.3)	—
XVIf	DMF	290	75	$C_{31}H_{22}N_5ClO_2$††	12.0 (13.1)	—
XVIg	DMF	290	70	$C_{32}H_{24}N_6O_3$	14.9 (15.6)	—
XVIh	DMF	295	80	$C_{31}H_{22}N_8O_6$	17.8 (18.6)	—

*All the compounds gave satisfactory C and H analyses.
†Found: Cl, 15.0. Calc.: Cl, 15.7%.
‡Found: Br, 16.9. Calc.: Br, 17.4%.
§Found: Br, 17.7. Calc.: Br, 18.1%.
**Found: Br, 15.3. Calc.: Br, 16.0%.
††Found: Cl, 6.6. Calc.: Cl, 6.8%.

Acidic cyclization of Ig. Formation of VI

The thiosemicarbazide derivative Ig (0.01 mol) was added with stirring to conc. H_2SO_4 (20 ml) during 30 min. The mixture was heated in an oil-bath at 120° for 20 min, and the slurry poured into ice-water. The separated solid was filtered and recrystallized from an appropriate solvent to give VI (Table 1); IR: 3300-3100 (−NH−), 3000 (CH, aromatic), 2850 (CH, aliphatic), 1640 (C=O), 1610, 1570 (C=N), 1480 (def. CH_2), 1320 (NCSN), 1000, 950 and 850 (phenyl groups).

Basic cyclization of Ig: Formation of VII

A mixture of Ig (0.01 mol) and aq. NaOH (10%, 50 ml) was heated under reflux for 2 hr and acidified with dil. HCl. The solid obtained was filtered to give VII (Table 1); IR: 3020 (CH, aromatic), 2910 (CH, aliphatic), 2620 (SH), 1680-1640 (C=O), 1580 (C=N), 1480 (def. CH_2), 1350 (NCSN), 1000, 950 and 800 (phenyl groups).

Preparation of VIII

A mixture of Ig (0.01 mol), monochloroacetic acid (0.01 mol) and anhyd. NaOAc (0.02 mol) in ethanol (25 ml) was heated under reflux for 5 hr on a water-bath. Ethanol was distilled off and the reaction mixture poured onto crushed ice. The solid obtained was filtered, washed with water and recrystallized from an appropriate solvent to give VIII (Table 1); IR: 3220 (NH), 3010 (CH, aromatic), 2900 (CH, aliphatic), 1710 (C=O, phthalazine), 1680 (C=O, thiazolidine), 1640 (C=O, acetic hydrazide), 1570 (C=N), 1480 (def. CH_2), 1350 (thiazolidine), 1000, 950and 800 (phenyl rings).

Cyclization of Ii: Formation of IX

Compound Ii (0.01 mol) was added to an aq. solution of NaOH (2*N*, 100 ml) and the reaction mixture refluxed for 4 hr, cooled and acidified with dil. HCl. The resultant solid was filtered and recrystallized from an appropriate solvent to give IX (Table 1); PMR: 2.5 (2H, q, CH_2−NH), 3.5 (2H, t, CH_2−CO− of pyrazolone), 4.7 (2H, s, CH_2−CO− of side chain), 7.5 (5H, m, C_6H_5), 7.8 (4H, m, C_6H_4) and 8.4 (1H, t, NH, exchangeable with D_2O).

Condensation of Ic with aldehydes, ketones and oxo-acids: Formation of Xa-l

To a solution of Ic (0.01 mol) in ethanol (95%, 25 ml) were add the appropriate aldehyde, ketone, mono-oxime or oxo-acid (0.01 mol) in ethanol (95%, 25 ml) and a few drops of gl. acetic acid. The reaction mixture was refluxed for 2 hr, left overnight and diluted with cold water. The solid obtained was filtered and recrystallized from an appropriate solvent to give X (Table 1); IR of Xa: 3480 (OH), 3200 (NH), 3020 (CH, aromatic), 2920 (CH, aliphatic), 1720-1640 (2C=O), 1580 (C=N), 1500 (def. CH_2), 1090 (Ph−O−Me), 1020, 1000 and 800 (phenyl groups); IR of Xj: 3200 (NH), 3010 (CH, aromatic), 2950 (CH, aliphatic), 1750-1650 (C=O), 1580 (C=N), 1480, 1440 (def. CH_2), 1000, 940 and 800 (phenyl groups).

Cyclization of Xb, Xd, Xg, Xh and Xi: Formation of XIIa-e

A mixture of Xb, Xd, Xg, Xh or Xi (0.01 mol) and the hydrazino compound XI (0.01 mol) in ethanol (100 ml) containing some drops of piperidine was heated under reflux for 10 hr, cooled and poured onto ice-HCl. The solid thus obtained was filtered and recrystallized from an appropriate solvent to give XII (Table 1); IR of XIId: 3400 (NH), 3300 (NH), 3050 (CH, aromatic), 2920 (CH, aliphatic), 1680 (C=O), 1590 (C=N), 1500 (def. CH_2), 1400 (pyridine ring), 1250 triazine ring), 1030, 1020, 1010 and 820 (phenyl rings); PMR of XIId: 2.5 (3H, s, CH_3), 3.3 (2H, s, CH_2), 6.8 (4H, m, C_5H_4 pyridine moiety), 7.3 (5H, m, C_6H_5 phenylphthalazine), 7.8 (4H, m, benzo), 7.9-8.1 (10H, m, aromatic protons of 1,2,4-triazine) and 8.7 (2H, d, NH−NH of tetrazine ring, exchangeable with D_2O).

Benzil monohydrazone (XIII)

Compound Ic (0.01 mol) was suspended in abs. ethanol-gl. AcOH mixture (50 ml) and benzil added to it in a slight excess. The reaction mixture was refluxed for 3 hr on a water-bath and cooled. The solid separated was filtered and recrystallized from an appropriate solvent to give XIII (Table 1).

Cyclization of XIII: Formation of XIV

To a solution of sodium ethylate (prepared by dissolving 0.23 g sodium in 20 ml abs. ethanol) was added XIII and the reaction mixture refluxed for 2 hr. The solid obtained upon dilution and acidification was filtered and recrystallized from an appropriate solvent to give XIV (Table 1).

Reaction of 2-benzoylbenzoic acid with Ic: Formation of XV

A mixture of Ic (0.01 mol) and *o*-benzoylbenzoic acid (0.01 mol) in gl. acetic acid (50 ml) was refluxed for 3 hr, concentrated under reduced pressure and cooled in ice. The resulting solid was filtered, washed with water and recrystallized from an appropriate solvent to give XV (Table 1); IR: 3020 (CH, aromatic), 2880 (CH, aliphatic), 1700-1630 (C=O), 1590 (C=N), 1470-1440 (def. CH_2), 1020, 970, 900 and 790 (phenyl groups); PMR: 3.4 (2H, s, CH_2−N), 7.8-7.7 (8H, m, benzo groups) and 7.9-8.5 (10H, m, phenyl protons).

Reactions of Ic with unsymmetrical 1,3-*bicarbonyl compounds: Formation of XVIa-l*

To a solution of Ic (0.01 mol) in gl. acetic acid (100 ml) was added the appropriate unsymmetrical 1,3-bicarbonyl compound (0.01 mol) and the reaction mixture refluxed for 2 hr and diluted with cold water. The solid obtained was filtered and crystallized from an appropriate solvent to give XVI (Table 1); IR of XVIe: 3020 (CH, aromatic), 2900 (CH, aliphatic), 1700-1640 (C=O), 1610-1590 (C=N), 1480 (def. CH_2), 1000, 920 and 800 (phenyl groups); IR of XVIg: 3300-3200 (−NH−NH−), 3020 (CH, aromâtic), 2950 (CH, aliphatic), 1700-1630 (C=O), 1580 (C=N), 1470 (def. CH_2), 1000, 970, 900 and 800 (phenyl groups); PMR of XVIe: 1.8 (3H, s, CH_3), 2.5 (2H, s, CH_2), 3.4 (1H, s, =CH of pyrazole), 7.6 (5H, m, C_6H_5), 7.8 (5H, m, aromatic protons) and 8.3 (4H, m, aromatic protons).

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Synthesis and reactions of phthalazine derivatives: Part II—Nucleophilic substitution and ring closure reactions of 1(2*H*)-oxo-4-phenyl-phthalazine-2-acetic acid hydrazide

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The reactions of 1(2*H*)-oxo-4-phenylphthalazine-2-acetic acid hydrazide (I) with halo compounds such as ethyl chloroformate, monochloroacetic acid, dichloroacetic acid, chloroacetaldehyde diethyl acetal, chloroacetyl chloride, phenacyl bromide, chloroacetamide and acetylene tetrachloride and those of 1(2*H*)-oxo-4-phenylphthalazine-2-acetic acid N^2-carbethoxyhydrazide (II) with primary amines such as *o*-phenylenediamine, hydrazine hydrate, thiosemicarbazide, aminoguanidine and guanidine hydrochloride have been studied in alkaline medium. The compounds isolated have been identified as N^1-hetero-N^2-substituted acetylhydrazine and diheterocyclic methane derivatives on the basis of elemental analysis, IR and PMR spectral data.

In the present study we have investigated the behaviour of 4-phenyl-1(2*H*)-oxophthalazine-2-acetic acid hydrazide (I)[1] and its carbethoxy derivative (II) towards nucleophilic substitution and cyclization reactions in alkalin medium.

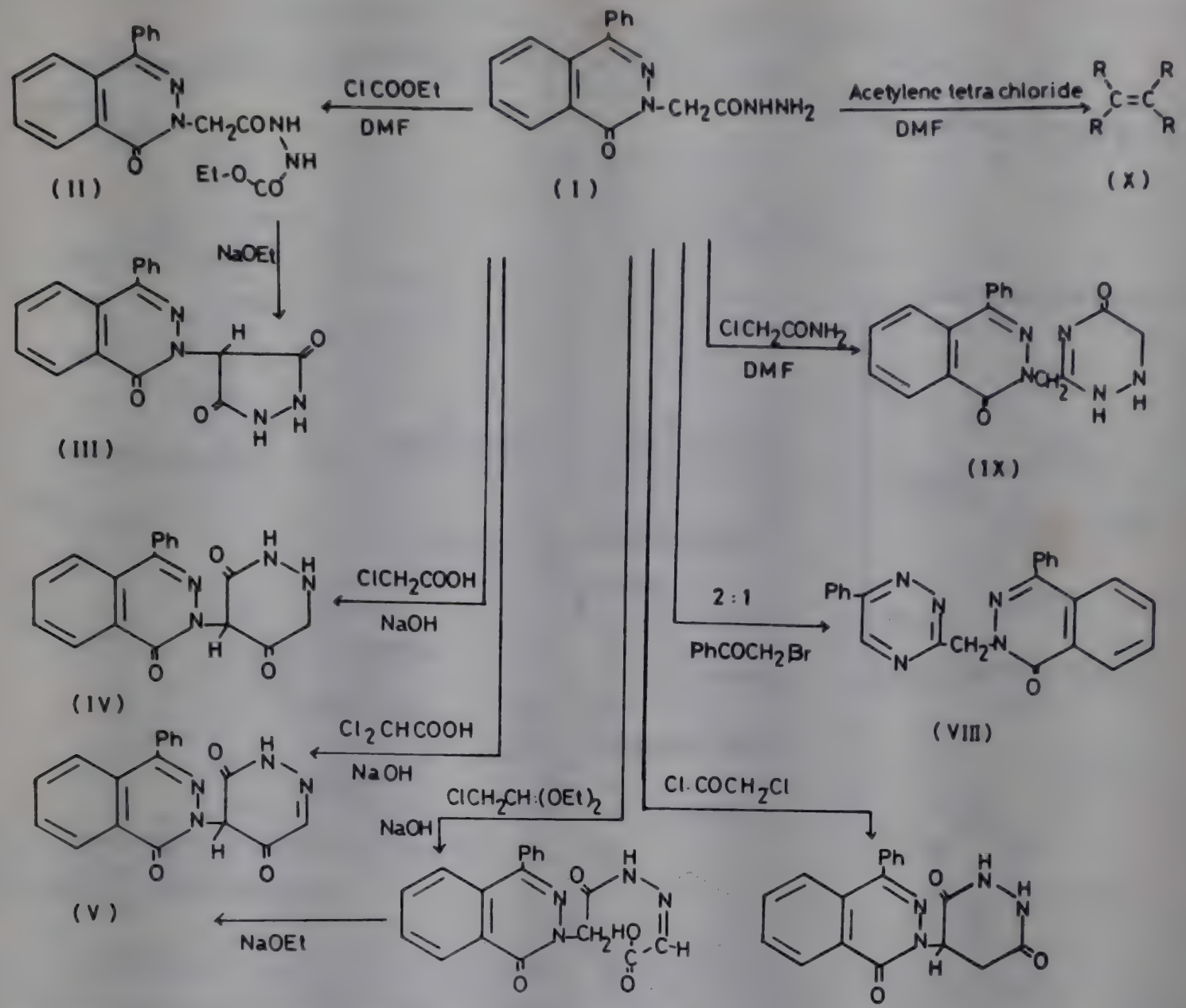
Treatment of I with ethyl chloroformate in the presence of DMF gave the corresponding ethyl ester (II) which underwent cyclization on heating with sodium ethoxide to give 4-[1(2*H*)-oxo-4-phenylphthalazin-2-yl]pyrazolidine-3,5-dione (III).

Compound I also reacted with halo compounds[2] such as monochloroacetic acid, dichloroacetic acid and chloroacetyl chloride in the presence of aq. sodium hydroxide to afford hexahydro-4-[1(2*H*)-oxo-4-phenylphthalazine-2-yl]pyridazine-3,5-dione (IV), hexahydro-4-[1(2*H*)-oxo-4-phenylphthalazine-2-yl]pyridazine-3,5-dione (V) and hexahydro-4-[1(2*H*)-oxo-4-phenylphthalazine-2-yl]pyridazine-3,6-dione (VI) respectively, while refluxing of I with chloroacetaldehyde diethyl acetal in the presence of aq. sodium hydroxide yielded the hydrazonoacetic acid (VII) which underwent cyclization with sodium ethoxide to give V, the structure of which was confirmed by elemental analysis, spectral data and direct comparison (m.m.p.) with the product obtained from I and dichloroacetic acid. Compound I on refluxing with phenacyl bromide (2:1)[3] in the presence of ethanol or with chloroacetamide in the presence of DMF[4] for a long time gave 6-phenyl-3-(substituted methyl)-1,2,4-triazine (VIII) or 1,2,5,6-tetrahydro-3-(substituted methyl)-1,2,4-triazine-5-one (IX), while treatment of I with acetylene tetrachloride in DMF gave the corresponding acetylenetetrabis(acetylhydrazine) derivative (X) (Scheme 1).

On the other hand, fusion of acetic acid N^2-carbethoxyhydrazide derivative (II) with *o*-phenylenediamine at 200° gave acetic acid N^2-(benzimidazol-2-yl)hydrazide (XI) while refluxing of II with hydrazine hydrate gave N^4-(substituted acetamido)semicarbazide (XII) which underwent cyclization by losing one mole of water to give 1,2,3,4-tetrahydro-6-(substituted methyl)-1,2,4,5-tetrazin-3-one (XIII), while acylation of XII with ethyl chloroformate in DMF led to the formation of N^1-carbethoxy-N^4-(substituted acetamido)semicarbazide (XIV) which when heated above its m.p. gave hexahydro-1-(substituted acetyl)-1,2,4,5-tetrazine-3,6-dione (XV).

The reaction of thiosemicarbazide with II in ethanol under reflux gave N^1-(thiocarbamyl)-N^4-(substituted acetamido)semicarbazide (XVI). Basic cyclization[5] of XVI using aq. sodium hydroxide afforded 3-mercapto-5-(substituted acetic acid hydrazido)-4*H*-triazole (XVII). However, acidic cyclization of XVI using conc. H_2SO_4 led to the formation of 2,3,4,5-tetrahydro-5-(thiocarbamyl)-6-(substituted methyl)-1,2,4,5-tetrazin-3-one (XVIII).

A similar treatment of II with aminoguanidine bicarbonate and guanidine hydrochloride[6] gave N^1-(substituted acetyl)-N^4-guanyl)semicarbazides XIX and XX respectively. Compound XIX underwent cyclization on heating with sodium ethoxide affording 3-amino-5-(substituted acetic acid hydrazido)-s-triazole (XXI), while XX on heating with gl. acetic acid[7] for a long time gave directly the tetrazepine derivative XXII (Scheme 2).



R=4-Phenyl-1-oxo-2H-phthalazin-2-acetic-acid hydrazon.

Scheme 1

All the compounds containing carbonyl groups other than that present in the phthalazinone moiety were insoluble in NaOH which confirmed their existence in ketonic form[8].

Experimental Procedure

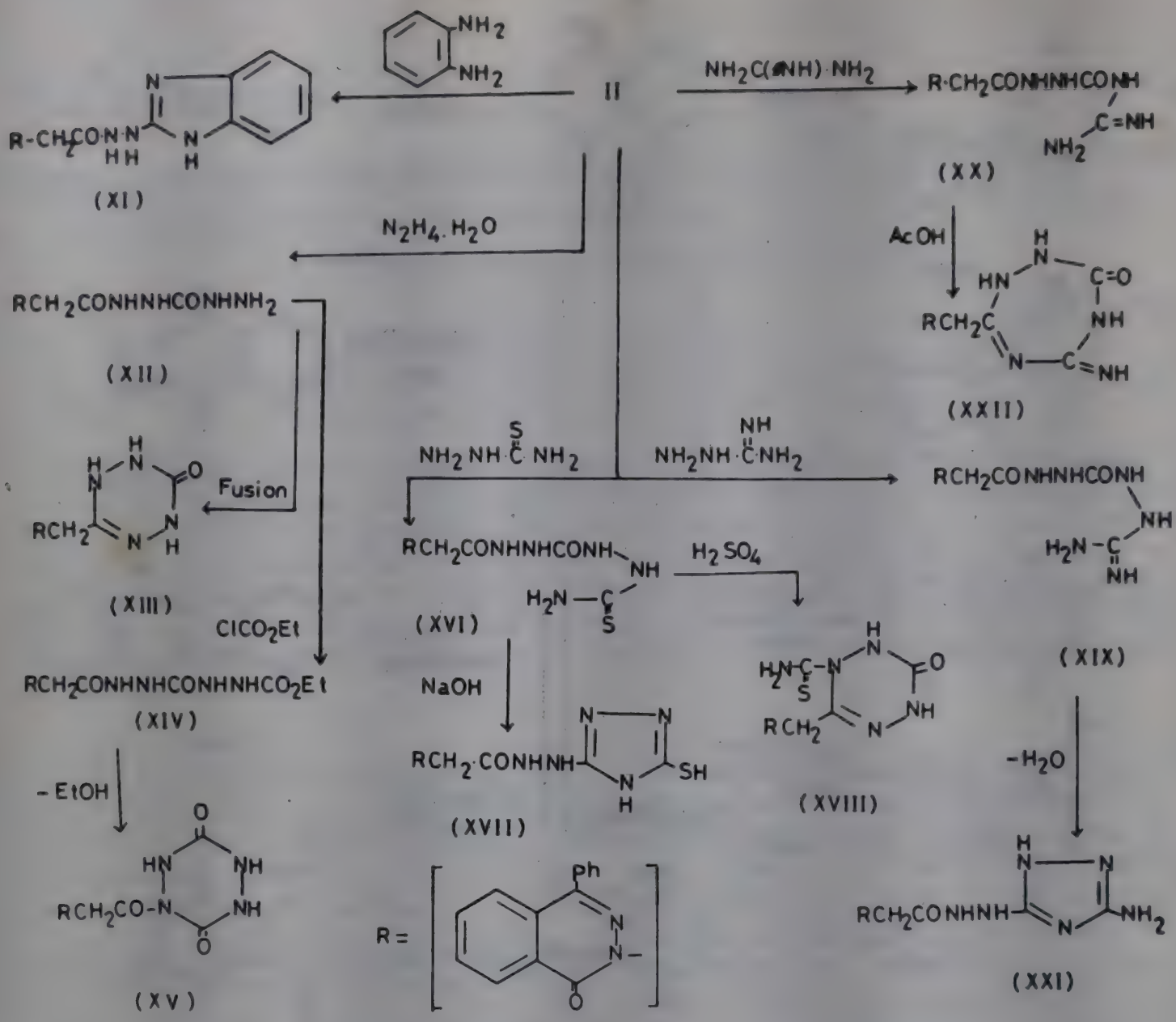
Melting points are uncorrected. Purity of the compounds was checked by paper chromatography using chloroform-ethyl acetate (9:1) as irrigant. IR spectra were recorded in KBr on a Pye-Unicam SP 1100 infrared spectrophotometer (ν_{max} in cm^{-1}) and PMR spectra in DMSO-d_6 on a Varian EM-390 90 MHz NMR spectrometer using TMS as internal standard (chemical shifts in δ, ppm). 1(2*H*)-Oxo-4-phenylphthalazine-2-acetic acid hydrazide (I) was prepared by us as described in a previous publication[1].

1(2H)-Oxo-4-phenylphthalazine-2-acetic acid N^2-carbethoxyhydrazide (II)

A mixture of I (0.01 mol) and ethyl chloroformate (0.01 mol) in DMF (10 ml) was heated under reflux for 15 min, cooled and acidified with dil. HCl. The solid obtained was filtered and recrystallized from an appropriate solvent to give II (Table 1); IR: 3400-3200 (−NH−NH), 1780-1760 (phthalazinone C=O), 1710-1650 (ethyl carboxylate and $-CH_2CONH-$ carbonyl), 1590 (C=N), 1050 (ether $-CO-OC_2H_5$) and 1000 (phenyl group); PMR: 1.5 (t, 3H, CH_3), 3.6 (s, 2H, CH_2N), 4.2-4.4 (q, 2H, CH_2-CH_3), 5.2 (s, 1H, CH=C(OH)−) and 5.9 (s, 1H, $-\underset{\displaystyle OH}{\underset{|}{CH}}-$) (as tautomocric structure), 7.6 (m, 4H, Ar−H), 8.2 (m, 5H, C_6H_5) and 8.7-9.5 (s, 2H, NH−NH, exchangeable with D_2O).

Cyclization of II: Formation of 4-[1(2H)-oxo-4-phenylphthalazin-2-yl]pyrazolidine-3,5-dione (III)

To a solution of sodium ethylate (prepared by dissolving 0.23 g sodium in 20 ml abs. ethanol) was added II and the reaction mixture refluxed for 2 hr. The solid, obtained upon dilution and acidification



Scheme 2

of the reaction mixture, was filtered and recrystallized from an appropriate solvent to give III (Table 1); IR: 3300 (NH), 1720 (C=O), 1660-1640 (2C=O) and 1570 (C=N).

Preparation of IV, V, VI and VII

An equimolecular mixture of I and monochloroacetic acid, dichloroacetic acid, chloroacetyl chloride or chloroacetaldehyde diethyl acetal in aq. NaOH solution (10%, 100 ml) was heated under reflux for 2 hr, cooled, diluted with water, and the resultant solid obtained filtered and recrystallized from an appropriate solvent to give IV, V, VI or VII (Table 1). IR (IV): 3300-3100 (NH−NH), 1750 (phthalazinone C=O), 1680-1630 (2C=O of pyridazinedione) and 1580 (C=N); PMR: 2.6 (2H, s, CH_2), 4.9 (1H, s, −COCHCO−), 7.5 (5H, m, C_6H_5), 7.8 (4H, m, C_6H_4 of phthalazine moiety) and 8.4 (1H, d, NH, exchangeable with D_2O). IR (V): 3380 (NH), 1740 (phthalazinone CO), 1680-1640 (2C=O of pyridazinedione) and 1575 (C=N); PMR: 3.7 (1H, s, −N=CH−CO−), 4.8 (1H, d, −CO−CH−CO−), 7.5 (5H, m, C_6H_5), 7.9 (4H, m, C_6H_4 of phthalazine moiety) and 8.4 (1H, s, NH, exchangeable with D_2O). IR (VII): 3480 (OH), 3330 (NH), 1720 (phthalazinone CO), 1680-1650 (2C=O), 1580 (C=N); gave acidity test with bicarbonate solution.

Cyclization of VII: Formation of V

To a solution of sodium ethylate (prepared by dissolving 0.23 g sodium in 20 ml abs. ethanol) was added VII and the reaction mixture refluxed for 2 hr, diluted and acidified. The solid obtained was filtered and recrystallized from an appropriate solvent to give V, identical (m.p. and m.m.p.) with that obtained alove.

6-Phenyl-3-(substituted methyl)-1,2,4-triazine (VIII)

A mixture of I (0.2 mol) and phenacyl bromide (0.1 mol) in ethanol (20 ml) containing a few drops of DMF was heated under reflux for 10 hr. The solid that separated after cooling was filtered and recrystallized from an appropriate solvent to give VIII (Table 1); IR: 1750 (phthalazinone CO), 1640-1620

Table 1—Characterization data of the various compounds prepared

Compd	Crystallized from	m.p. °C	Yield (%)	Mol. formula	N (%)*	
					Found	Calc.
II	Ethanol	180	80	$C_{19}H_{18}N_4O_4$	15.0	15.3
III	Ethanol	170	70	$C_{17}H_{12}N_4O_3$	17.1	17.5
IV	Acetic acid	196	75	$C_{18}H_{14}N_4O_3$	16.1	16.8
V	DMF	215	65	$C_{18}H_{12}N_4O_3$	16.2	16.9
VI	Acetic acid	200	80	$C_{18}H_{14}N_4O_3$	16.5	16.8
VII	Dil. ethanol	195	85	$C_{18}H_{14}N_4O_4$	15.3	16.0
VIII	Methanol	180	90	$C_{24}H_{17}N_5O$	17.5	17.9
IX	Ethanol	175	80	$C_{18}H_{15}N_5O_2$	20.8	21.0
X	DMF	290	95	$C_{66}H_{52}N_{16}O_8$	18.3	18.7
XI	Ethylbenzene	220	75	$C_{23}H_{18}N_6O_2$	19.9	20.5
XII	Ethanol	207	90	$C_{17}H_{16}N_6O_3$	23.4	23.9
XIII	Acetic acid	285	70	$C_{17}H_{14}N_6O_2$	24.5	25.1
XIV	Chloroform	180	75	$C_{20}H_{20}N_6O_5$	19.2	19.8
XV	Acetic acid	215	65	$C_{18}H_{14}N_6O_4$	21.9	22.2
XVI†	Ethanol	193	90	$C_{18}H_{17}N_7SO_3$	23.5	23.8
XVII	Methanol	179	80	$C_{18}H_{15}N_7O_2$	26.8	27.1
XVIII‡	Ethanol	157	65	$C_{18}H_{15}N_7SO_2$	24.4	24.9
XIX	Ethanol	190	80	$C_{18}H_{18}N_8O_3$	28.0	28.4
XX	Ethylbenzene	174	70	$C_{18}H_{17}N_7O_3$	25.6	25.9
XXI	Ethanol	218	80	$C_{18}H_{16}N_8O_2$	29.0	29.8
XXII	Acetic acid	190	60	$C_{18}H_{15}N_7O_2$	26.8	27.1

*All the compounds gave satisfactory C and H analyses.
†Found: S, 7.5. Calc.: S, 7.8%.
‡Found: S, 7.9. Calc.: S, 8.2%.

(triazine C=N), 1590 (phthalazine C=N); PMR: 4.5 (s, 2H, $>N-CH_2-N<$), 5.2 (s, 1H, 1,2,4-triazine CH=N), 7.7 (s, 4H, Ar−H) and 7.9-8.2 (m, 10H, $2C_6H_5$).

1,2,5,6-*Tetrahydro*-3-(*substituted methyl*)-1,2,4-*triazin*-5-*one* (*IX*)

An equimolecular mixture of I and chloroacetamide in DMF (20 ml) was heated under reflux for 12 hr. The solid that separated after cooling and dilution was filtered and recrystallized from an appropriate solvent to give IX (Table 1).

Reaction of I with acetylene tetrachloride. Formation of X

A mixture of I (0.01 mol) and acetylene tetrachloride (0.01 mol) in DMF (20 ml) was heated under reflux for 4 hr, cooled and diluted with water. The solid obtained was filtered and recrystallized from an appropriate solvent to give X (Table 1).

N^2-(*Benzimidazol*-2-*yl*)*acetic acid hydrazide* (*XI*)

A mixture of II (0.01 mol) and *o*-phenylenediamine (0.01 mol) was heated at 200° in an oil-bath for 15 min. The solid obtained was triturated with methanol and crystallized from an appropriate solvent to give XI (Table 1); IR: 3400-3100 (NH−NH), 3100 (NH bonded), 1750 (phthalazinone C=O), 1650 (−CO−NH), 1610, 1580 (2C=N).

Preparation of XII

A mixture of II (0.01 mol) and hydrazine hydrate (0.01 mol) in ethanol (50 ml) was heated under reflux for 4 hr. The solid obtained after cooling was filtered and recrystallized from an appropriate solvent to give XII (Table 1).

Cyclization of XII: Formation of XIII

Compound XII was heated at 200° in an oil-bath for 15 min. The solid obtained was triturated with methanol and crystallized from an appropriate solvent to give XIII (Table 1); IR: 3200-3100 (−NH−NH−), 1700 (phthalazinone C=O), 1650 (tetrazinone C=O), 1590, 1570 (C=N).

Acylation of XII:Formation of XIV

A mixture of XII (0.01 mol) and ethyl chloroformate (0.01 mol) in DMF (10 ml) was heated under reflux for 15 min, cooled and acidified with dil. HCl. The solid obtained was filtered and recrystallized from an appropriate solvent to give XIV (Table 1).

Cyclization of XIV: Formation of XV

Compound XIV was heated above its melting point in an oil-bath for 15 min. The solid obtained was triturated with methanol and crystallized from an appropriate solvent to give XV (Table 1); IR: 3420-3320 (−NH−NH−), 3120 (NH), 1730 (phthalazinone C=O), 1680-1640 (2C=O of tetrazinedione).

Reaction of II with thiosemicarbazide: Formation of XVI

An equimolar mixture of II and thiosemicarbazide (in hot water containing a few drops of AcOH) in ethanol (100 ml) was heated under reflux for 2 hr and cooled. The solid obtained was filtered and recrystallized from an appropriate solvent to give XVI (Table 1); IR: 3320-3120 (NH−NH), 3100 (NH), 1750 (phthalazinone C=O), 1670-1650 (C=O of acid hydrazide and semicarbazide moieties), 1570 (C=N), 1340 (NCSN)[9], 1200 (C=S).

Basic cyclization of XVI: Formation of XVII

A mixture of XVI (0.01 mol) and aq. NaOH (10%, 50 ml) was heated under reflux for 2 hr and acidified with dil. HCl. The solid obtained was filtered and recrystallized from an appropriate solvent to give XVII (Table 1); IR: 3400-3300 (NH−NH), 3150 (NH), 2500 (SH), 1720 (phthalazinone C=O), 1670-1650 (CONH), 1570 (C=N) and 1330 (−NCSN−).

Acidic cyclization of XVI: Formation of XVIII

The thiosemicarbazide derivative XVI (0.01 mol) was added with stirring to conc. H_2SO_4 (20 ml) during 30 min and the reaction mixture heated in an oil-bath at 120° for 20 min and the slurry poured into ice-water. The separated solid was filtered and recrystallized from an appropriate solvent to give XVIII (Table 1); IR: 3420 (NH_2), 3300-3270 (NH), 2500 (SH), 1700 (phthalazinone C=O), 1680-1640 (tetrazinone C=O), 1570 (C=N) and 1320 (−N−CS−N−).

Reaction of II with aminoguanidine bicarbonate and guanidine hydrochloride: Formation of XIX and XX

A suspension of aminoguanidine bicarbonate or guanidine hydrochloride (0.01 mol) in water (10 ml) and II (0.01 mol) in DMF (100 ml) was heated under reflux for 4 hr, cooled and diluted with water. The solid obtained was filtered and recrystallized from an appropriate solvent to give XIX or XX (Table 1).

Cyclization of XIX: Formation of XXI

To a solution of sodium ethylate (prepared by dissolving 0.23 g sodium in 20 ml abs. ethanol) was added XIX and the reaction mixture refluxed for 2 hr, diluted and acidified. The solid obtained was filtered and recrystallized from an appropriate solvent to give XXI (Table 1); IR: 3450 (NH_2), 3300-3200 (NH−NH), 3150 (NH), 1750 (phthalazinone C=O), 1680-1640 (−CONH.NH−), 1600 (C=N), 1570 (C=N), 1330-1310 and 1080-1060 [N−C(NH)N][10].

Cyclization of XX: Formation of XXII

To gl. AcOH (50 ml) was added XX (0.01 mol) and the mixture heated for 10 hr, cooled, and the solid separated filtered and recrystallized from an appropriate solvent to give XXII (Table 1).

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Studies on 1,4-dihydropyrazolo[4,3-*e*][1,3,4]oxadiazine hemiaza-di(tri)carbocyanine dyes

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New asymmetrical 3,6-bis[2(4)-hemiaza-di(tri)carbocyanine]dyes (IVa-c, VIa-d) incorporating 1,4-dihydropyrazolo[4,3-*e*][1,3,4]oxadiazine moiety have been prepared and their structures established by spectral data. Their electronic spectra in buffer solutions have been utilised to select the optimal *p*H value at which they can be applied as photosensitisers. Some of the dyes have been tested for their antimicrobial activity. The structure activity relationship has also been discussed.

Although a large number of cyanine dyes have been prepared earlier and their applications investigated[1-6], those containing a 1,4-dihydropyrazolo-[4,3-*e*][1,3,4]oxadiazine moiety have not been reported in the literature. Recently[7] the synthesis and antimicrobial activity of pyrazolo[3,4-*d*]quinoxaline dimethine cyanine dyes have been reported from this laboratory. In the present study some new 1,4-dihydropyrazolo[4,3-*e*][1,3,4]oxadiazine cyanine dyes containing the hemiazadi(tri)carbocyanine moiety have been prepared with the hope that such dyes might exhibit photosensitisation effect or enhanced bacteriostatic activity.

The starting compound 1,4-dihydro-3,6-dimethyl-1-phenylpyrazolo[4,3-*e*][1,3,4]oxadiazine (II) was prepared by the interaction of equimolar amounts of 4-bromo-3-methyl-1-phenylpyrazol-5(4*H*)-one (I)[6] with hydrazine in Ac_2O followed by fusion of the product above its melting point.

The structure of II was established by elemental analysis and IR and PMR spectral data[9,10].

The desired asymmetrical 1,4-dihydro-1-phenylpyrazolo[4,3-*e*][1,3,4]oxadiazine-3,6-bis-[2(4)-hemiazadicarbocyanine]dyes IVa-c were obtained by the following routs. Selective oxidation of II with selenium dioxide[11] in ethanol afforded the 3-formyl derivative (III) which on reaction with two mol equivalent of 2-methylquarternary salts gave the corresponding asymmetrical hemiazadicarbocyanine dyes (IVa-c; Scheme 1).

The structures III and IV were established by elemental analyses (Table 1) and IR and PMR spectral data.

The dyes (IV) were highly coloured compounds (violet/blue) and soluble in most of organic solvents exhibiting green fluorescence. They were soluble in conc. H_2SO_4 liberating iodine vapours on warming. Their ethanolic solutions gave violet colour in alkaline medium which discharged on acidification.

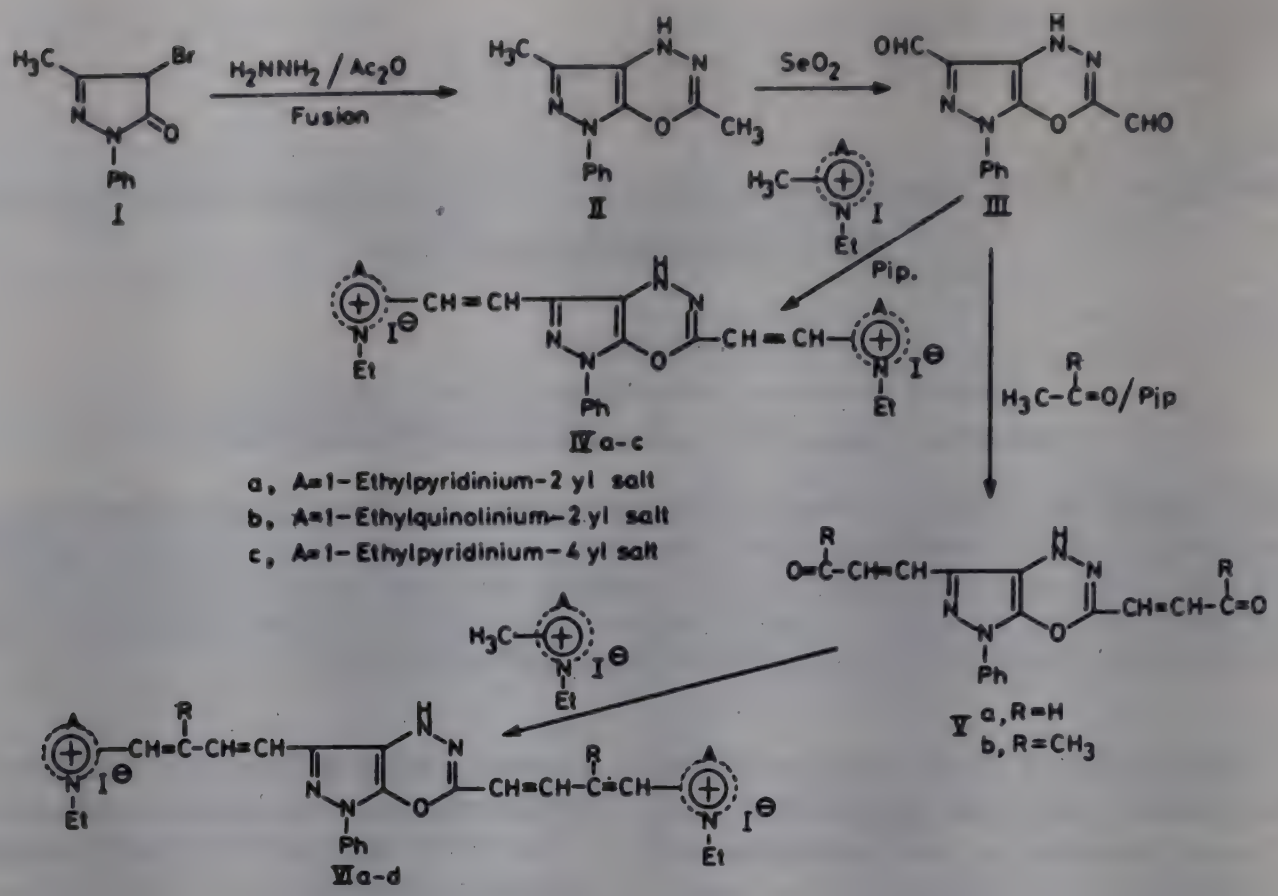
The visible spectra of IVa-c in 95% ethanol exhibited absorption bands which became intense and strong red-shifted on increasing the conjugation of quarternary heterocyclic residues (**A**). For example, IVa (A= 1-ethylpyridinium-2yl salt) showed an absorption band at 480 nm (ε_{max} 3200 $dm^3\ mol^{-1}\ cm^{-1}$). On substituting the pyridyl nucleus by quinoline (IVb), there appeared two absorption bands at 505 and 585 nm (ε_{max} 16400 and 7000 $dm^3\ mol^{-1}$ respectively). On the other hand substitution of 1-ethylpyridinium 4yl salt for (**A**) caused a red shift by 10 nm (IVc: λ_{max} 490 nm, ε_{max} 6300 $dm^3\ mol^{-1}\ cm^{-1}$).

Interaction of III with two mol equivalent of acetaldehyde or acetone in the presence of piperidine as catalyst and ethanol as solvent afforded the corresponding 3,6-bis(β-acetylethylidene) derivatives (Va,b). The reaction of Va,b with methyl quaternary salts gave the corresponding asymmetrical 1,4-dihydro-1-phenylpyrazolo[4,3-*e*][1,3,4]oxadiazine-3,6-bis[2(4)-hemiazadicarbocyanine]dyes (VIa-d; Scheme 1).

The structures V and VI were established by elemental analyses (Table 1) and IR and PMR spectral data.

The dyes VI were highly coloured compounds (intense violet) and soluble in most of organic solvents exhibiting intense green fluorescence. They were soluble in conc. H_2SO_4 liberating iodine vapours on warming. Their ethanolic solutions gave a violet colour in alkaline medium which discharged on acidification.

The visible spectra of VIa-d in 95% ethanol exhibited absorption bands which became intense and strong red-shifted on increasing the conjugation of quarternary heterocyclic residue (**A**) or substituting R = CH_3. For example, VIa (A= 1-ethylpyridinium-2yl salt;



Scheme 1

Table 1 – Characterisation data of 1,4-dihydro-1-phenylpyrazolo[4,3-*e*][1,3,4]oxadiazine 3,6-bis[(4)-hemiazadi- or tri-carbocyanine]dyes (IVa-c, VIa-d)

Compd	Colour	m.p. °C	Yield (%)	Molecular formula (mol wt)	Found (%) (Calc.)			Spectra λ_{max} (ε_{max})
					C	H	N	
IVa	Reddish violet	153-55	40	$C_{28}H_{28}N_6OI_2$ (718)	47.0 (46.8	4.1 3.9	11.9 11.7)	480 (3200)
IVb	Intense blue	184-86	58	$C_{36}H_{32}N_6OI_2$ (818)	53.0 (52.8	4.0 3.9	10.5 10.3)	505 (16400), 585 (7000)
IVc	Reddish violet	180-82	32	$C_{28}H_{28}N_6OI_2$ (718)	47.0 (46.8	3.8 3.9	11.8 11.7)	490 (6300)
VIa	Intense violet	164-66	30	$C_{32}H_{32}N_6OI_2$ (770)	50.0 (49.9	4.5 4.2	11.1 10.9)	520 (16500), 585 (19350)
VIb	Bluish violet	196-98	45	$C_{40}H_{36}N_6OI_2$ (870)	55.4 (55.2	4.2 4.1	9.9 9.7)	540 (17700), 585 (21400)
VIc	Brownish violet	172-74	33	$C_{32}H_{32}N_6OI_2$ (770)	50.1 (49.9	4.4 4.2	11.1 10.9)	530 (17250), 585 (20000)
VId	Blue crystals	210-12	52	$C_{42}H_{40}N_6OI_2$ (898)	56.2 (56.1	4.7 4.5	9.6 9.4)	565 (19500), 585 (22000)

R = H) showed absorption bands at 520 and 585 nm (ε_{max} 16500 and 19350 dm^3 mol^{-1} cm^{-1}, respectively). On substituting the pyridyl nucleus with quinoline, a bathochromic shift of 20 nm was observed (VIb; λ_{max} 540 and 585 nm; ε_{max} 17700 and 21400 dm^3 mol^{-1} cm^{-1}, respectively). Similarly, substitution of 1-ethylpyridinium-4yl salt for (**A**) caused a red shift of 10nm (VIc: λ_{max} 530 and 585 nm; ε_{max} 17250 and 20000 dm^3 mol^{-1} cm^{-1}, respectively). On the other hand, replacement of CH_3 group for R intensified and

shifted the band towards longer wavelength (VId: λ_{max} 565 and 585 nm; ε_{max} 19500 and 22000 $dm^3\ mol^{-1}\ cm^{-1}$, respectively).

A comparison of the absorption spectra of hemiazadicarbocyanine dyes IV with those of hemiazatricarbocyanine dyes VI, indicates that for the same substituent for **A** the absorption band of VI undergoes a bathochromic shift of 35-40 nm but its intensity also increase compared to that of IV (cf. Table 1).

The ethanolic solutions of some selected hemiazadi-(tri)carbocyanine dyes (IVb and VIb) gave a violet colour in basic medium which discharged on acidification. This prompted me to study the effect of different *p*H values on the spectral behaviour of selected cyanines (IVb and VIb) in order to permit selection of a suitable *p*H at which the compounds could be applied as photosensitizers. Thus, the electronic spectra of IVb and VIb in aq. solutions of varying *p*H (2.40-12.16) showed a bathochromic shift in their absorption band in alkaline media (high *p*H), Fig. 1. This bathochromic shift is mainly due to a relatively increased negative charge on NH and N-phenyl groups of pyrazolo[4,3-*e*][1,3,4]oxadiazine moiety. On the other hand, this band is hypsochromically shifted in acidic media (low *p*H). This is due to the fact that NH group becomes protonated in solutions of low *p*H and therefore the CT interaction with the protonated form is expected to be difficult. However, as the *p*H of the medium increase, the NH group becomes more deprotonated and therefore its mesomeric interaction with the rest of the molecule becomes high, consequently the CT interaction within the free base is facilitated.

The absorbance of CT band in compounds IVb and VIb increases with increasing *p*H. The variation of absorbance with *p*H values can be utilized for determining the ionisation constants of the dyes[12]. Thus, by plotting the absorbance at λ_{max} vs *p*H, S-shaped curves were obtained (Fig. 2). The horizontal portion of S-curves corresponds to the acidic form of the compounds while the upper portion to the right corresponds to the basic form. Since pK_a is defined as the *p*H value for which one half of the compound is in the basic form and the other half in the acidic form, this point is determined by intersection of the S-curve with a horizontal line midway between the left and right segments. From S-curve (Fig. 2), the pK_a values for the compounds IVb and VIb were found to be 6-9 and 6-8.5, respectively.

Biological activity

The antimicrobial activity of some selected cyanine dyes (IVa-c and VIa-c) was determined against the bacteria *Bacillus stearothermophilus* (gram + ve), *Salmonell sp.* and *Pscudomones sp.* (gram − ve) and the fungi *Mahranchea puchella var sulfurea*, *Talaronyces* dupmti and *Aspergillus funigatus* employing the filter paper disc method[13] at 100 ppm concentration in ethylene glycol. The results are given in Table 2.

The structure activity relationship was studied relative to the parent compound 1,4-dihydro-3,6-dimethyl-1-phenylpyrazolo[4,3-*e*][1,3,4]oxadiazine (II) which was active against fungi and the bacteria, *Bacillus stearothermophilus* and inactive against other bacterial strains. Oxidation of the methyl group in II to a carboxaldehyde function (III) rendered the compound inactive against bacterial and fungal strains. Incorporation of quinolinin-2-yl salts in II (as in IVb) enhanced the biological activities more than pyridinium-2(4)-yl salts (compounds IVa and IVc). Extending conjugation of heterocyclic quarternary salts as in com-

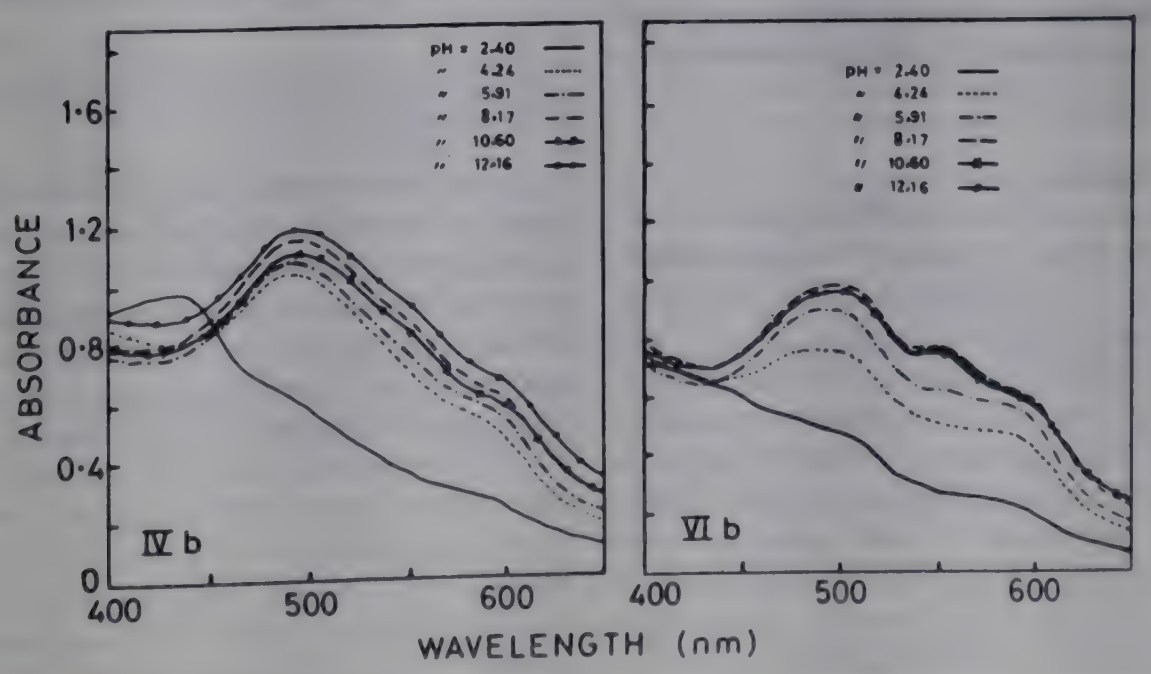


Fig. 1 – Electronic absorption spectra of IVb and VIb in aq. universal buffer solutions (concentration: 2×10^{-4} *M*)

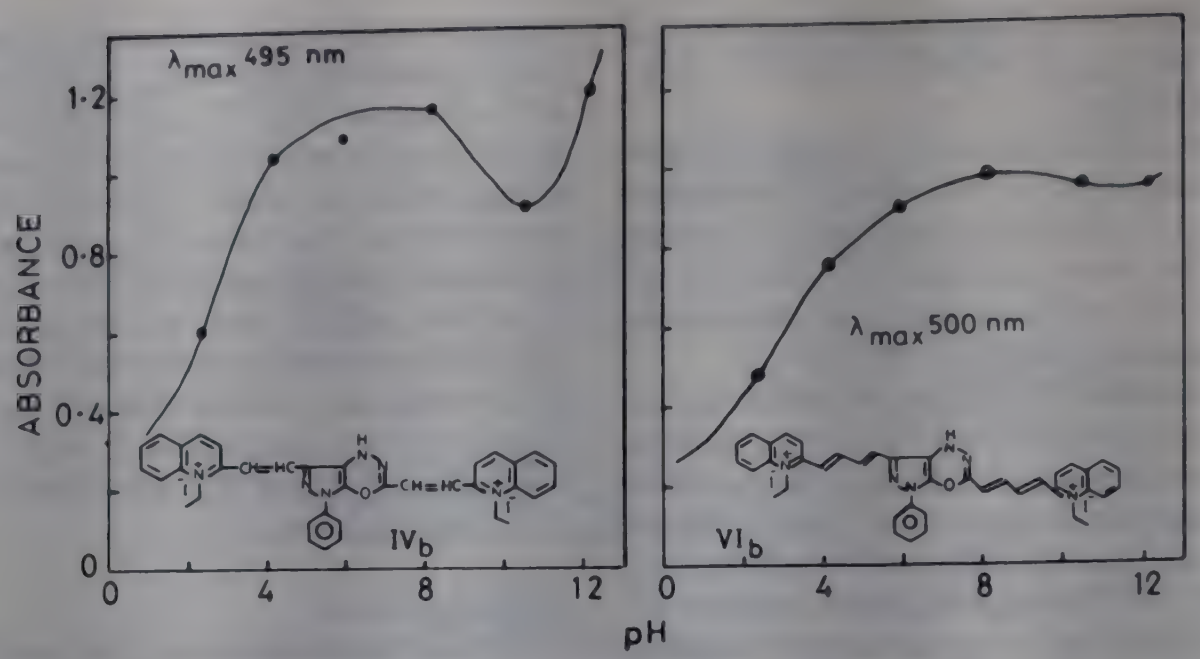


Fig. 2 – Relation between absorbance and *p*H (S-curves)

Table 2 – Antimicrobial screening results* of selected compounds

Organism used	Compound							
	II	III	IVa	IVb	IVc	VIa	VIb	VIc
	Bacterial strains							
Bacillus stearothermophilus	13	—	—	17	—	31	12	25
Salmonella sp.	—	—	—	10	—	—	—	12
Pseudomonas sp.	—	—	—	—	—	—	—	—
	Fungal strains							
Mabranches puchella var *sulfurea*	14	—	—	20	—	30	13	28
Talaromyces dupmti	10	—	—	16	—	20	11	25
Aspergillus fumigatus	10	—	9	22	23	30	10	29

*Inhibition zones in mm.

pound VIb increased the potency. Thus, quinolinium-2-yl salt hemiazatricarbocyanine (VIb) was more potent than the analogues containing pyridinium-2(4)-yl salts (VIa,c) and quinolinium-2-yl salt hemiazadicarbocyanine (IVb).

Experimental Procedure

Melting points are uncorrected. IR spectra were recorded on a Perkin-Elmer infrared 127B spectrophotometer (ν_{max} in cm^{-1}), visible spectra on a Unicam Sp 1750 ultraviolet spectrophotometer (λ_{max} in nm) and PMR spectra on a 90 MHz EM 390 NMR spectrophotometer using TMS as internal standard (chemical shifts in δ, ppm). Aqueous universal buffer solutions of *p*H range 2.40-12.16 were prepared as described in literature[14]. The *p*H values of these solutions were checked at 25° using an Orion *p*H meter model 60/A accurate to ± 0.005 *p*H units. Ethanolic solution (0.5 ml, 2×10^{-4} *M*) of IVb or VIb was added to buffer solution (4.5 ml).

4-Bromo-3-methyl-1-phenylpyrazol-5(4*H*)-one (I) was prepared following the literature method[8].

1,4-*Dihydro*-3,6-*dimethyl*-1-*phenylpyrazolo*[4,3-*e*]-[1,3,4]*oxadiazine* (*II*)

Equimolecular amounts of I (0.01 mol) and hydrazine hydrate (0.01 mol) were dissolved in Ac_2O and the solution was refluxed for 3 hr, filtered hot, the filtrate concentrated to half its volume, cooled and poured into ice cold water. The precipitated product was filtered and crystallised from acetic acid to give 4-acetylhydrazino-3-methyl-1-phenylpyrazol-5-one (m.p. 273-75°) which was fused for 5-15 min, triturated with abs. ethanol and then reprecipitated by dilution with water to give II, m.p. 152°, yield 70% (Found: C, 63.3; H, 6.0; N, 24.8. $C_{12}H_{12}N_4O$ requires C, 63.2; H, 5.3; N, 24.6%); IR(KBr): 1150, 1090 (oxadiazine C – O – C), 1590 (C = N), 3490 (NH); PMR ($CDCl_3$): 7.5-8.3 (m, 5H, Ar – H), 1.6 (s, 3H, pyrazole CH_3), 1.4 (s, 3H, oxa-

diazine CH_3), 3.4 (s, 1H, NH, exchangeable with D_2O).

1,4-*Dihydro*-1-*phenylpyrazolo*[4,3-*e*][1,3,4]-*oxadiazine*-3,6-*dicarboxaldehyde* (*III*)

A mixture of II (0.01 mole) and selenium dioxide (0.026 mole) in ethanol (20 ml) was refluxed for 12-15 hr and filtered to remove the deposited selenium. The product obtained after concentration and cooling of the filterate, was filtered and crystallised from ethanol to give III as brownish crystals, m.p. 132°, yield 56% (Found: C, 56.4; H, 3.3; N, 22.0; $C_{12}H_8N_4O_2$ requires C, 56.3; H, 3.1; N, 22.0%), IR(KBr): 1665 (aldehydic C=O), 1150, 1090 (oxadiazine C−O−C), 1590 (C=N), 3490 (NH); PMR($CDCl_3$): 7.6-8.5 (m, 5H, Ar−H), 9.6 (s, 2H, 2×CHO), 3.6 (s, 1H, NH, exchangeable with D_2O).

1,4-*Dihydro*-1-*phenylpyrazolo*[4,3-*e*][1,3,4]*oxadiazine*-3,6-*bis*-2(4)-*hemiazadicarbocyanines* (*IVa-c*)

A mixture of III (0.01 mole) and 2-methylquaternary salt (α-picoline, quinaldine or γ-picoline ethiodide; 0.02 mole) was dissolved in ethanol (30 ml) and piperidine (1 ml) added to it. The reaction mixture was refluxed for 12-20 hr, filtered hot, the filtrate concentrated to half its volume, cooled, acidified with a few drops of acetic acid and diluted with water. The precipitated product was filtered and crystallised from aq. ethanol to give IV (Table 1). The spectral data of IVb are as follows: IR(KBr): 2990-2940 (ethiodide of heterocyclic residue), 1150, 1090 (cyclic C−O−C), 1590 (C=N), 3490 (NH); PMR($CDCl_3$): 7.5-8.3 (m, 17H, Ar−H), 5.4 (t, 4H, olefinic protons), 2.7 (q, 4H, 2×NCH_2), 4.3 (t, 6H, 2×CH_3), 3.6 (s, 1H, NH, exchangeable with D_2O).

3,6-*Bis*(β-*acylethylidene*)-1-*phenylpyrazolo*[4,3-*e*]-[1,3,4]*oxadiazines* (*Va,b*):

To a solution of III (0.01 mole) and acetaldehyde or acetone (0.02 mole) in ethanol (30 ml) was added piperidine (1 ml) and the reaction mixture refluxed for 5-8 hr, concentrated to half its volume, cooled, acidified with a few drops of acetic acid and diluted with water. The precipitated product was filtered and crystallised from aq. ethanol to give Va or Vb. Their characterisation data are as follows: Va − m.p. 142-45°, yield 45% (Found: C, 62.5; H, 4.0; N, 18.3. $C_{16}H_{12}N_4O_3$ requires C, 62.3; H, 3.9; N, 18.2%) IR(KBr): 1620 (α,β-unsaturated C=O), 1150, 1090 (cyclic C−O−C), 1590 (C=N), 3490 (NH); PMR($CDCl_3$): 7.3-8.2 (m, 5H, Ar−H) 5.8 (s, 2H, olefinic protons), 9.4 (s, 4H, 2×CHO and 2×CH), 3.65 (s, 1H, NH, exchangeable with D_2O). Vb—m.p. 160-62°, 52% (Found: C, 64.5; H, 4.9; N, 16.9. $C_{18}H_{16}N_4O_3$ requires C, 64.3; H, 4.8; N, 16.7%).

1,4-*Dihydro*-1-*phenylpyrazolo*[4,3-*e*][1,3,4]*oxadiazine*-3,6-*bis*[2(4)-*hemiazatricarbocyanines*] (*VIa-d*)

To a solution of Va or Vb (0.01 mole) and the 2-methylquaternary salt (0.02 mole) in ethanol (30 ml) was added piperidin (1 ml) and the reaction mixture refluxed for 12-15 hr and worked up in the same way as described for IV (*vide supra*) to get VI (Table 1). The cyanine dyes thus prepared were crystallized from aq. ethanol. The spectral data of VIb are as follows: IR(KBr): 2990-2940 (ethiodide of heterocyclic residue), 1600 (conjugated C=C), 3490 (NH), 1590 (C=N); PMR($CDCl_3$): 7.6-8.5 (m, 17H, Ar−H), 5.85 (q, 8H, olefinic protons), 4.3 (t, 6H, 2×CH_3), 2.6 (q, 4H, 2×N−CH_2), 3.7 (b, 1H, NH, exchangeable with D_2O).

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Side-chain bromination of osthol using N-bromosuccinimide and some related reactions

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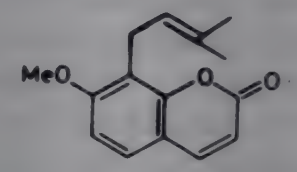
Osthol when treated with N-bromosuccinimide under free radical conditions gives 8-(3-bromomethyl-2-butenyl)-7-methoxycoumarin (**2**), whereas under ionic conditions the product obtained is 8-(2-bromo-3-hydroxy-3-methylbutyl)-7-methoxycoumarin (**5**) which on reaction with sodium borohydride affords osthol epoxide (**7**) (meranzin). The epoxide **7** is converted back into the bromohydrin (**5**) by the action of HBr in dioxane and to 8-(2-amino-3-hydroxy-3-methylbutyl)-7-methoxycoumarin (**8**) by the action of ammonia.

A five-carbon unit attached to the benzene ring, generally in the form of an isoprenoid side-chain, is a characteristic feature of many naturally occurring coumarins. One such compound is osthol (**1**) which is 7-methoxy-8-(γ,γ-dimethylallyl)coumarin. The selective modification of the olefinic double bond of osthol, without simultaneously bringing about changes in the coumarin moiety, has been the subject of several past investigations[1-7]. In the present work, we have examined the action of N-bromosuccinimide on osthol under two sets of conditions.



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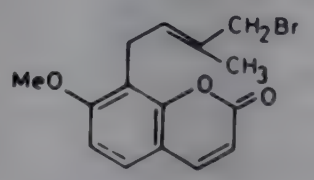

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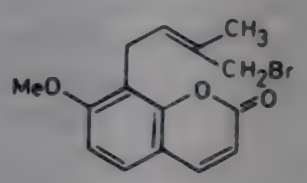

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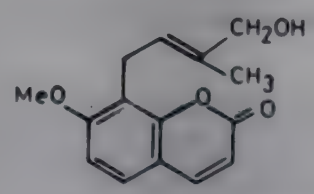

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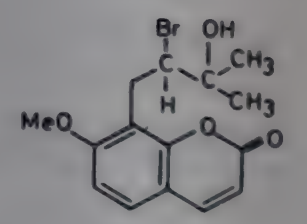

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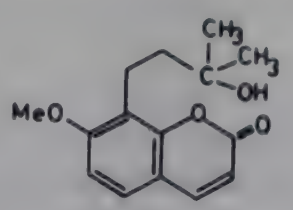
Reaction of osthol with N-bromosuccinimide under free radical conditions

Under controlled and designed conditions, N-bromosuccinimide can bring about bromination at allylic or benzylic sites. There are three such positions in osthol. However, when osthol was treated with N-bromosuccinimide in dry carbon tetrachloride under reflux, in the presence of dibenzoyl peroxide, only one product was obtained. The presence of a single bromine atom in the compound was shown by the 1:1 ratio of the (M^+):$(M+2)$ peaks in its mass spectrum. The molecular ion peak appeared at m/z 322 and the $(M+2)$ peak at 324. The base peak appeared at m/z 243 and there was no corresponding $(M+2)$ peak clearly showing the facile loss of a bromine atom from the molecular ion. Its PMR spectrum exhibited signals attributable to protons at C-3 (δ 6.28, d, $J_{3,4}$ = 9.5 Hz), C-4 (δ 7.88, d, $J_{4,3}$ = 9.5 Hz), C-5 (δ 7.44, d, $J_{5,6}$ = 8.5 Hz) and C-6 (δ 7.00, d, $J_{6,5}$ = 8.5 Hz) as well as the olefinic proton at C-2′ (δ 5.7, t) and the benzylic protons at C-1′ (δ 4.3, m) suggesting that bromination had occurred on one of the two geminal methyl groups. A careful examination of the δ 2 to 4.5 region showed the presence of only one methyl group besides the O-methyl group in the compound. The methyl protons appeared at δ 2.0 as a singlet and the signal at δ 3.6 (d) was attributed to the methylene protons. On the basis of the foregoing (**2**) and (**3**) analysis, two structures, **2** and **3** could be considered for the bromo compound.

On the basis of the following considerations, the product was assigned the structure **2**. The double bond has the *E*-configuration in this structure and

the bromine atom is as far away as possible from the oxygen atoms of the coumarin moiety. In **3**, in certain conformations at least, considerable electrostatic repulsion between the electronegative bromine atom and the oxygen functions could be expected, resulting in reduced stability of the structure. While (**2**) is a new compound, the corresponding carbinol [arnottinin methyl ether (**4**)] is known and its PMR data are available in literature[6]. The PMR data for **2** are in close agreement with those recorded for **4**, allowing for the expected differences due to substitution of the OH group by bromine. Special mention may be made here of the signal due to the olefinic proton which appeared at δ 5.7 in the spectrum of **2**, comparable to its position (δ 5.5) in **4**.



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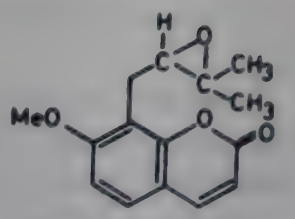

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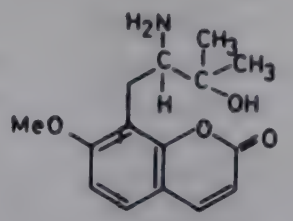

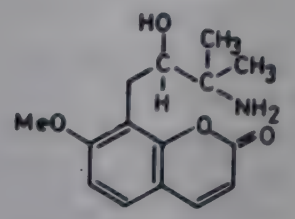

Reaction of N-bromosuccinimide in dimethyl sulphoxide

N-Bromosuccinimide can also be used for the preparation of bromohydrins in high yields, using dimethyl sulphoxide (containing a little water) as the reaction medium[8]. Thus, when osthol was treated at room temperature with NBS in dimethyl sulphoxide to which 1% water had been added a monobromo compound with a molecular weight of 340 was obtained. In the mass spectrum of this compound there was a prominent peak at m/z 282 due to the loss of a molecule of acetone from the molecular ion. Subsequent loss of a bromine atom is presumably responsible for the base peak at m/z 203. These data suggested the structure **5** for the product. This structure was also supported by other spectral data as well as by mechanistic considerations.

The IR soectrum of the compound showed a broad absorption at 3420 characteristic of hydroxyl group and a strong absorption at 1710 cm^{-1} due to the lactone carbonyl. The PMR spectrum of the compound showed signals at δ 1.47 (s, 6H, *gem*-dimethyl), 3.47 (m, 2H, benzylic CH_2), 4.44 (dd, 1H, C_2-H), 2.99 (s, 1H, $-OH$), 3.9 (s, 3H, $-OCH_3$), 6.19 (d, 1H, $J_{3,4} = 9.5$ Hz, C_3-H), 6.8 (d, 1H, $J_{6,5} = 8.5$ Hz, C_6-H), 7.33 (d, 1H, $J_{5,6} = 8.5$ Hz, C_5-H) and 7.55 (d, 1H, $J_{4,3} = 9.5$ Hz, C_4-H).

With the objective of converting the bromohydrin (**5**) into the tertiary carbinol (**6**), compound **5** was treated with sodium borohydride in dimethylsulphoxide. The spectral data however showed that the product was not the expected carbinol (**6**) but the epoxide (**7**). Thus, the mass spectrum had the molecular ion peak at m/z 260 and the base peak at m/z 131; bromine was absent. The identity of the compound was confirmed by a direct comparison (m.m.p., IR) with an authentic sample[1]. Compound **7** could be reconverted into the bromohydrin (**5**) by treatment with 48% HBr in dioxane. The transformation obviously involves an S_N2 type ring opening of the oxirane ring. The exclusive formation of **5** in this reaction rules out a step-wise mechanism. In the S_N2 type mechanism, the bromine ion attacks the less sterically hindered carbon atom of the epoxide ring, bringing about a regiospecific opening, leading to **5**, which is the product obtained in the reaction.

In a related experiment a solution of the epoxide in dioxane was treated with ammonia when a single product was obtained. Its IR spectrum showed a broad absorption at 3440 cm^{-1} attributable to OH group; apparently the bands due to the symmetric and asymmetric stretchings of the amino function are submerged under this broad band. The PMR spectrum was in complete agreement with the structure **8** and not **9**.

Thus, the signal due to the *gem*-dimethyl group appeared at δ 1.40 (s, 6H) and that attributable to the methine-H at 3.76 (m, 1H). Other signals were observed at δ 3.6 (m, 2H, benzylic CH_2), 3.16 (m, 2H, $-NH_2$), 4.04 (s, 3H, $-OCH_3$), 6.4 (d, 1H, $J_{3,4} = 9.5$ Hz, C_3H), 7.08 (d, 1H, $J_{6,5} = 8.5$ Hz, C_4-H), 7.56 (d, 1H, $J_{5,6} = 8.5$ Hz, C_5-H) and 7.84 (d, 1H, $J_{4,3} = 9.5$ Hz, C_6-H). The formation of **8** can be readily explained, in mechanistic terms, as the result of an S_N2 type ring opening of the oxirane ring with ammonia attacking the less hindered carbon atom.

Experimental Procedure

Melting points were determined in a sulphuric acid-bath and are uncorrected. UV spectra were recorded on a Perkin-Elmer UV/Vis Lamda-5 spectrophotometer, IR spectra on a Perkin-Elmer PE 283 spectrophotometer, PMR spectra on a JEOL MH-100 or a JEOL Fx-90 Q NMR spectrometer using TMS as internal standard, and mass spectra on a VG Micromass 7070 H mass spectrometer. Elemental analyses were carried out in a Herrmann-Moritz Macanil-10 instrument.

8-(2-*Bromomethyl*-2-*butenyl*)-7-*methoxycoumarin* (**2**)

A solution of osthol (240 mg, 1 mmol) in dry carbon tetrachloride (20 ml) containing N-bromosuccinimide (200 mg, 1 mmol) and dibenzoyl peroxide (10 mg) was refluxed for 30 min. After the removal of succinimide which had separated, the clear solution was concentrated to obtain the product as a pale yellow solid. Purification by chromatography over a column of silica gel yielded colourless needles (200 mg), m.p. 121-22° (Found: C, 55.3; H, 4.7. $C_{15}H_{15}BrO_3$ requires C, 55.9; H, 4.7%); UV (MeOH): 218, 240, 252 and 312 nm; IR(KBr): 1720(s), 1610(s), 1565(m), 1500(m), 1440(m), 1380(m), 1275(m), 1250(s) and 1115(s) cm^{-1}; PMR (90 MHz, $CDCl_3$): δ 2.0 (s, 3H), 3.6 (d, 2H), 4.0 (s, 3H), 4.30 (m, 2H), 5.7 (t, 1H), 6.28 (d, 1H, J = 9.5 Hz), 7.00 (d, 1H, J = 8.5 Hz), 7.44 (d, 1H, J = 8.5 Hz), 7.88 (d, 1H, J = 9.5 Hz); MS: m/z 324 (28%), 322(28), 243(100), 213(10), 211(15), 190(10), 189(88), 187(11), 175(10), 159(12), 131(21), 115(10), 89(8), 77(11), 63(10).

8-(2-*Bromo*-3-*hydroxy*-3-*methylbutyl*-7-*methoxycoumarin* (**5**)

A solution of osthol (240 mg, 1 mmol) in dimethyl sulphoxide (15 ml) containing water (1 ml), was treated with N-bromosuccinimide (350 mg, 2 mmol) and the mixture stirred at room temperature for 1 hr. The reaction mixture was poured into water (100 ml) with stirring when a solid separated out. It was collected and purified by chromatography over a column of silica gel, which afforded needles (180 mg), m.p. 152-54° (Found: C, 52.9; H, 5.2. $C_{15}H_{17}BrO_4$ requires C, 52.9; H, 5.0%); UV (MeOH): 215, 240 and 324 nm; IR(KBr): 3440(broad), 1710(s), 1600(s), 1590(s), 1490(m), 1460(s), 1380(m), 1260(s), 1240(s) and 1120(m) cm^{-1}; PMR (90 MHz, $CDCl_3$): δ 1.47 (s, 6H), 2.99 (s, 1H), 3.47 (m, 2H), 3.90 (s, 3H), 4.44 (m, 1H), 6.19 (d, 1H, J = 9.5 Hz), 6.8 (d, 1H, J = 8.5 Hz), 7.33 (d, 1H, J = 8.5 Hz), 7.55 (d, 1H, J = 9.5 Hz); MS: m/z 342(31), 340(31), 327(10), 284(52), 282(52), 260(11), 243(30), 203(100), 204(20), 190(15), 189(35), 131(20), 59(20).

Conversion of the bromohydrin (**5**) *into osthol epoxide* (**7**)

To a solution of **5** (200 mg, 0.6 mmol) in dry dimethyl sulphoxide (10 ml), sodium borohydride (10 mg) was added at 20°. The reaction mixture was maintained at this temperature overnight and worked-up in the usual manner. Osthol epoxide was obtained as a colourless powder (120 mg), m.p. 96-98° (Found: C, 68.9; H, 6.2. Calc. for $C_{15}H_{16}O_4$ C, 69.2; H, 6.1%); IR(KBr): 1710(s), 1610(s), 1535(m), 1500(m), 1440(m), 1380(m), 1260(m), 1250(s), 1096(s) cm^{-1}; PMR (100 MHz, $CDCl_3$): δ 1.22 (s, 3H), 1.44 (s, 3H), 3.1 (m, 2H), 4.0 (s, 3H), 6.32 (d, 1H, J = 9.5 Hz), 6.96 (d, 1H, J = 8.5 Hz), 7.48 (d, 1H, J = 8.5 Hz), 7.76 (d, 1H, J = 9.5 Hz); MS: m/z 260(25%), 219(18), 217(27), 203(32), 202(100), 201(18), 190(30), 189(60), 187(70), 178(15), 174(20), 159(10).

Reconversion of osthol epoxide into the bromohydrin (**5**)

The mixture obtained by cautious addition of 48% hydrobromic acid (0.5 ml) to a solution of the epoxide (**7**) (130 mg, 0.5 mmol) in dioxane (10 ml), was heated on a water-bath for 30 min. Work-up and subsequent purification by preparative thin layer chromatography yielded the bromohydrin as crystalline plates (80 mg), m.p. 151-52°, identical in all respects with **5** described earlier.

Action of ammonia on compound **7**

To a solution of the epoxide (**7**) (260 mg 1 mmol) in dioxane (10 ml) was added aq. ammonia (2 ml, sp. gr. 0.91) and the mixture stirred at 100° for 2 hr. Work-up and subsequent purification by preparative thin layer chromatography yielded **8** as colourless crystals (90 mg), m.p. 176-78°; UV (MeOH): 210, 257, 322 nm; IR(KBr): 3440-3200 (broad), 1710(s), 1610(s), 1500(m), 1460(m), 1280(m), 1250(s), 1100(s) cm^{-1}; PMR (100 MHz, $CDCl_3$): δ 1.4 (s, 6H), 3.16 (m, 2H), 3.6 (m, 2H), 3.76 (m, 1H), 4.04 (s, 3H), 6.4 (d, 1H, J = 9.5 Hz), 7.08 (d, 1H, J = 8.5 Hz), 7.56 (d, 1H, J = 8.5 Hz), 7.84 (d, 1H, J = 9.5 Hz).

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Synthesis and antiinflammatory activity of some 3-amino- and 3-trifluoroacetylamino-4,5-dihydro-1*H*-pyrazoles

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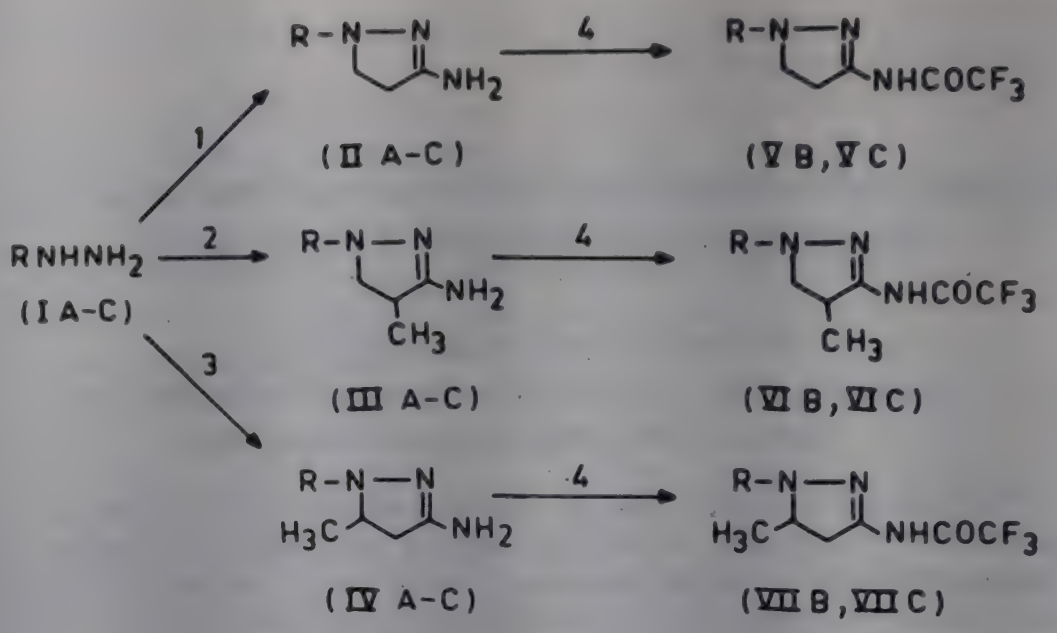
3-Amino-4,5-dihydro-1*H*-pyrazoles bearing 4-aryl-2-thiazolyl-(IIA), 2-benzothiazolyl-(IIB) and 4-methyl-2-quinolyl-(IIC) substituents at position-1, their 4- and 5-methyl analogues (IIIA-C and IVA-C) and 3-trifluoroacetylamino derivatives have been synthesized as potential antiinflammatory agents. Compounds IIA-C, IIIA-C and IVA-C have been obtained by the condensation of respective hydrazines with acrylonitrile, methacrylonitrile and crotonitrile, respectively and their trifluoroacetyl derivatives by treating the 3-amino compounds with trifluoroacetic anhydride. Some of the compounds show moderate to significant level of antiinflammatory activity.

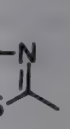
Almost all the non-steroidal antiinflammatory drugs (NSAIDS) under current clinical usage are highly acidic in nature and suffer from a common drawback of gastrointestinal toxicity, thus indicating a clear need to develop a non-acidic non-steroidal antiinflammatory agent. Following the reported antiinflammatory activity exhibited by several 3-amino-2-pyrazolines[1,2] and 3-aminopyrazoles and their trifluoroacetyl derivatives[3] and in continuation of our work on the synthesis of thiazole, benzothiazole and benzimidazole compounds of potential medicinal interest[4-9], we now report the synthesis of a series of 3-amino-2-pyrazolines such as 3-amino-1-(4-aryl-2-thiazolyl)-4,5-dihydro-1*H*-pyrazoles (IIA), their 4- and 5-methyl analogues (IIIA and IVA), 3-amino-1-(2-benzothiazolyl)-4,5-dihydro-1*H*-pyrazoles (IIB), their 4- and 5-methyl analogues (IIIB and IVB), and 3-amino-1-(4-methyl-2-quinolyl)-4,5-dihydro-1*H*-pyrazoles (IIC) and their 4- and 5-methyl analogues (IIIC and IVC) for evaluation as potential antiinflammatory agents. 3-Amino-2-pyrazolines were also converted to their trifluoroacetyl derivatives (VB-VIIB and VC-VIIC) for the same purpose. These compounds were synthesized according to the reaction sequences depicted in Scheme 1.

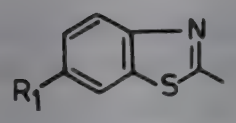
The reaction between arylhydrazines and α,β-unsaturated nitriles was studied in some detail[10]. It was observed that the course of reaction depended upon the reaction conditions employed resulting in the formation of different isomeric products. In the acidic medium, phenylhydrazine reacted with α,β-unsaturated nitriles at N-2 atom of the neutral molecule $PhNHNH_2$, whereas in the basic medium it reacted with N-1 atom of the conjugate base $Ph\bar{N}NH_2$. The course of reaction in the basic medium giving rise to 3-amino-4,5-dihydro-1*H*-pyrazoles is well documented and may be affected by the increased stability of the conjugate base due to the presence of a phenyl or aryl ring on negatively charged nitrogen atom. The required 2-hydrazino-4-arylthiazoles (IA)[11], 2-hydrazinobenzothiazoles (IB)[12,13] and 2-hydrazino-4-methylquinolines (IC)[14-16] were prepared following the known procedures.

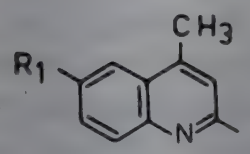
The key step in the synthesis of the compounds IIA-C, IIIA-C and IVA-C (Tables 1-3) involved condensation of heterocyclylhydrazines (IA-C) with acrylonitrile, methacrylonitrile and crotononitrile, respectively in ethanol in the presence of sodium ethoxide (obtained from sodium and ethanol) giving the desired 3-amino-4,5-dihydro-1*H*-pyrazoles in 48-70% yields. Treatment of 3-amino compounds (IIB, IIC, IIIB, IIIC, IVB and IVC) with trifluoroacetic anhydride in dry benzene yielded the corresponding trifluoroacetyl derivatives (VB, VC, VIB, VIC, VIIB and VIIC) in good yields (52-68%; Tables 4 and 5). The structures of these new compounds were confirmed by their IR, PMR and mass spectral data.

The IR spectra of IIA-C, IIIA-C and IVA-C showed characteristic bands in the regions 3480-3160 (NH str.) and 1640-1630 (C=N str. or NH bend). The IR spectra of their trifluoroacetyl derivatives (VB-VIIB and VC-VIIC) exhibited bands at 1200, 1170, 1120 due to CF_3 stretching vibrations in addition to absorptions in the region 3440-3180 (NH str.) and 1640-1630 (C=N str or NH bend). The PMR spectra of 3-amino-1-(4-aryl-2-thiazolyl)-4,5-dihydro-1*H*-pyrazoles (IIA)



A R = R_1 —  R_1 = H, Cl, Br

B R =  R_1 = H, CH_3, OCH_3, Cl

C R =  R_1 = H, OCH_3, Cl

1. $CH_2=CHCN$, Na/EtOH, Δ
2. $CH_2=C(CH_3)CN$, Na/EtOH, Δ
3. $CH_3CH=CHCN$, Na/EtOH, Δ
4. $(CF_3CO)_2O$, benzene

Scheme 1

showed signals in the regions δ 2.9-3.0 (t, 2H, pyrazole CH_2 at position-4), 3.9-4.0 (t, 2H, pyrazole CH_2 at position-5), 6.0-6.15 (s, 2H, NH_2) in addition to that for aromatic protons. The PMR spectra of their 4-methyl analogues (IIIA) showed signals at δ 1.3 (d, 3H, CH_3), 3.4 (m, 1H, pyrazole CH at position-4), 4.05-4.17 (m, 2H, pyrazole CH_2 at position-5), 6.15-6.35 (s, 2H, NH_2) and those of 5-methyl analogues (IVA) at 1.5 (d, 3H, CH_3), 3.2-3.3 (m, 2H, pyrazole CH_2 at position-4), 4.3-4.55 (m, 1H, pyrazole CH at position-5), 6.1-6.2 (s, 2H, NH_2) apart from signals for the aromatic protons.

The PMR spectra of IIB, IIC, IIIB, IIIC, IVB and IVC were similar and in conformity with the structures assigned.

Antiinflammatory activity

Selected compounds belonging to all the series of 3-amino- and 3-trifluoroacetylamino-4,5-dihydro-1*H*-pyrazoles prepared were subjected to preliminary screening for antiinflammatory activity by carrageenin-induced rat paw edema test according to the procedure of Winter *et al.*[17] as modified by Dhawan and Srimal[18] at 1/5th of their ALD_{50} dose level. Compounds of the series IIA-IVA showed only moderate activity, the highest activity (~32% inhibition) was shown by IVA_2 (R_1 = Cl). Compounds of the series IIB-IVB exhibited significant activity (30-50% inhibition) with IIA_1 (R = H) showing 50% inhibition. Compounds belonging to the quinolyl series IIC-IVC, however, exhibited activity of low order (20% inhibition).

Table 1 – Characterization data of 3-amino-1-(4-aryl-2-thiazolyl)-4,5-dihydro-1*H*-pyrazoles and their 4- and 5-methyl analogues (IIA, IIIA, IVA)

Compd	R_1	m.p. °C	Yield (%)	Mol. formula	Found (Calc.) %		
					C	H	N
IIA_1*	H	212	63	$C_{12}H_{12}N_4S$	58.5 (59.0	5.0 4.9	22.5 23.0)
IIA_2†	Cl	226	61	$C_{12}H_{11}ClN_4S$	51.3 (51.7	4.2 3.9	19.7 20.1)
IIA_3†	Br	215	59	$C_{12}H_{11}BrN_4S$	44.9 (44.6	3.8 3.4	16.9 17.3)
$IIIA_1$*	H	156	53	$C_{13}H_{14}N_4S$	60.1 (60.5	4.9 5.4	21.7 21.7)
$IIIA_2$†	Cl	179	48	$C_{13}H_{13}ClN_4S$	53.8 (53.3	4.6 4.4	19.5 19.1)
$IIIA_3$†	Br	187	51	$C_{13}H_{13}BrN_4S$	46.3 (46.3	3.7 3.9	16.6 16.6)
IVA_1*	H	163	58	$C_{13}H_{14}N_4S$	60.2 (60.5	5.1 5.4	22.1 21.7)
IVA_2†	Cl	197	52	$C_{13}H_{13}ClN_4S$	53.7 (53.3	4.8 4.4	19.3 19.1)
IVA_3†	Br	182	57	$C_{13}H_{13}BrN_4S$	46.5 (46.3	3.9 3.9	16.1 16.6)

*Solvent of crystallization was benzene-pet. ether.
†Solvent of crystallization was ethanol.
MS: (IIA_1): $M^{+\cdot}$, m/z 244. Calc. mol. wt 244.
(IIA_2): $M^{+\cdot}$), m/z 278/280. Calc. mol wt 278/280.
(IIA_3): $M^{+\cdot}$, m/z 322/324. Calc. mol. wt 322/324.
($IIIA_1$): $M^{+\cdot}$, m/z 258. Calc. mol. wt 258.
($IIIA_2$): $M^{+\cdot}$, m/z 292/294. Calc. mol. wt 292/294.
(IVA_1): $M^{+\cdot}$, m/z 258. Calc. mol. wt 258.

Table 2 – Characterization data of 3-amino-1-(2-benzothiazolyl-4,5-dihydro-1*H*-pyrazoles and their 4- and 5-methyl analogues (IIB, IIIB, IVB)

Compd	R_1	m.p. °C	Yield (%)	Mol. formula	N (%)	
					Found	Calc.
IIB_1*	H	218	65	$C_{10}H_{10}N_4S$	25.7	25.7
IIB_2†	CH_3	236	60	$C_{11}H_{12}N_4S$	24.4	24.1
IIB_3†	OCH_3	221	57	$C_{11}H_{12}N_4OS$	22.3	22.6
IIB_4*	Cl	272	53	$C_{10}H_9ClN_4S$	22.5	22.2
$IIIB_1$†	H	207	54	$C_{11}H_{12}N_4S$	23.9	24.1
$IIIB_2$†	CH_3	210	57	$C_{12}H_{14}N_4S$	22.3	22.8
$IIIB_3$†	OCH_3	175	55	$C_{12}H_{14}N_4OS$	21.5	21.4
$IIIB_4$†	Cl	190	53	$C_{11}H_{11}ClN_4S$	20.8	21.0
IVB_1†	H	208	61	$C_{11}H_{12}N_4S$	24.3	24.1
IVB_2†	CH_3	196	56	$C_{12}H_{14}N_4S$	22.5	22.8
IVB_3†	OCH_3	190	56	$C_{12}H_{14}N_4OS$	21.7	21.4
IVB_4†	Cl	224	52	$C_{11}H_{11}ClN_4S$	21.2	21.0

*Solvent of crystallization was ethanol.
†Compounds were crystallized from ethanol-water.
MS: (IIB_1): $M^{+\cdot}$, m/z 218. Calc. mol. wt 218.
(IIB_2): $M^{+\cdot}$, m/z 232. Calc. mol. wt 232.
($IIIB_1$): $M^{+\cdot}$, m/z 232. Calc. mol. wt. 232.
($IIIB_3$): $M^{+\cdot}$, m/z 262. Calc. mol. wt 262.
($IIIB_4$): $M^{+\cdot}$, m/z 266/268. Calc. mol. wt. 266/268.
(IVB_1): $M^{+\cdot}$, m/z 232. Calc. mol. wt 232.
(IVB_2): $M^{+\cdot}$, m/z 246. Calc. mol. wt 246.

Table 3 – Characterization data of 3-amino-1-(4-methyl-2-quinolyl)4,5-dihydro-1*H*-pyrazoles and their 4- and 5-methyl analogues (IIC, IIIC, IVC)

Compd*	R_1	m.p. °C	Yield (%)	Mol. formula	Found (Calc.) (%)		
					C	H	N
IIC_1	H	175	59	$C_{13}H_{14}N_4$	68.7	5.8	24.6
					(69.0	6.2	24.8)
IIC_2	OCH_3	228-30	70	$C_{14}H_{16}N_4O$	65.6	6.5	21.7
					(65.6	6.3	21.9)
IIC_3	Cl	110	62	$C_{13}H_{13}ClN_4$	60.3	5.1	21.0
					(59.9	5.0	21.5)
$IIIC_1$	H	199	60	$C_{14}H_{16}N_4$	70.1	6.6	23.5
					(70.0	6.7	23.3)
$IIIC_2$	OCH_3	190	57	$C_{15}H_{18}N_4O$	66.8	6.3	20.8
					(66.7	6.7	20.7)
$IIIC_3$	Cl	205	56	$C_{14}H_{15}ClN_4$	61.3	5.3	20.6
					(61.2	5.5	20.4)
IVC_1	H	187	53	$C_{14}H_{16}N_4$	70.2	6.2	23.8
					(70.0	6.8	23.3)
IVC_2	OCH_3	180	51	$C_{15}H_{18}N_4O$	66.6	7.1	21.0
					(66.7	6.7	20.7)
IVC_3	Cl	195	54	$C_{14}H_{15}ClN_4$	61.5	5.4	20.9
					(61.2	5.5	20.4)

*All the compounds were crystallized from benzene-pet. ether.
MS: (IIC_1): $M^{+\cdot}$, m/z 226. Calc. mol. wt 226.
($IIIC_1$): $M^{+\cdot}$, m/z 240. Calc. mol. wt 240.
(IVC_2): $M^{+\cdot}$, m/z 270. Calc. mol. wt 270.

Table 4 – Characterization data of 1-(2-benzothiazolyl-3-trifluoroacetylamino-4,5-dihydro-1*H*-pyrazoles and their 4- and 5-methyl analogues (VB, VIB, VIIB)

Compd*	R_1	m.p. °C	Yield (%)	Mol. formula	N (%)	
					Found	(Calc.)
VB_1	H	233	60	$C_{12}H_9F_3N_4OS$	17.5	17.8
VB_2	CH_3	238	68	$C_{13}H_{11}F_3N_4OS$	16.7	17.1
VB_3	OCH_3	169	57	$C_{13}H_{11}F_3N_4O_2S$	15.9	16.3
VB_4	Cl	232	59	$C_{12}H_8F_3ClN_4OS$	15.9	16.1
VIB_1	H	212	57	$C_{13}H_{11}F_3N_4OS$	16.6	17.1
VIB_2	CH_3	202	53	$C_{14}H_{13}F_3N_4OS$	16.5	16.4
VIB_3	OCH_3	208	56	$C_{14}H_{13}F_3N_4O_2S$	15.2	15.6
VIB_4	Cl	197	57	$C_{13}H_{10}ClF_3N_4OS$	15.1	15.4
$VIIB_1$	H	147	61	$C_{13}H_{11}F_3N_4OS$	16.6	17.1
$VIIB_2$	CH_3	185	68	$C_{14}H_{13}F_3N_4OS$	16.0	16.4
$VIIB_3$	OCH_3	172	63	$C_{14}H_{13}F_3N_4O_2S$	15.4	15.6
$VIIB_4$	Cl	132	60	$C_{13}H_{10}ClF_3N_4OS$	15.1	15.4

*Compounds were crystallized from ethanol-water.
MS: (VIB_1): $M^{+\cdot}$, m/z 328. Calc. mol. wt 328.

The trifluoroacetyl derivatives (VB-VIIB and VC-VIIC) exhibited activity of the same order as their parent 3-aminopyrazolines. Indomethacin showed 30-40% inhibition at 3-5 mg/kg and phenylbutazone 60% inhibition at 100 mg/kg dose levels under the same experimental conditions.

Experimental Procedure

Melting points were determined in open capillaries in a sulphuric acid-bath and are uncorrected. IR spectra were recorded as nujol mulls on a Beckman IR-20 spectrophotometer (ν_{max} in cm^{-1}), PMR spectra on a Perkin-Elmer R-32 (90 MHz)

Table 5 – Characterization data of 1-(4-methyl-2-quinolyl)-3-trifluoroacetylamino-4,5-dihydro-1*H*-pyrazoles and their 4- and 5-methyl analogues (VC, VIC, VIIC)

Compd*	R_1	m.p. °C	Yield (%)	Mol. formula	N (%)	
					Found	(Calc.)
VC_1	H	154	58	$C_{15}H_{13}F_3N_4O$	17.8	17.4
VC_2	OCH_3	140	62	$C_{16}H_{15}F_3N_4O_2$	15.9	15.9
VC_3	Cl	185	68	$C_{15}H_{12}ClF_3N_4O$	15.4	15.7
VIC_1	H	136	61	$C_{16}H_{15}F_3N_4O$	16.3	16.7
VIC_2	OCH_3	124	54	$C_{17}H_{17}F_3N_4O_2$	15.6	15.3
VIC_3	Cl	165	52	$C_{16}H_{14}ClF_3N_4O$	14.7	15.1
$VIIC_1$	H	128	53	$C_{16}H_{15}F_3N_4O$	16.3	16.7
$VIIC_2$	OCH_3	142	56	$C_{17}H_{17}F_3N_4O_2$	15.0	15.3
$VIIC_3$	Cl	178	57	$C_{16}H_{14}ClF_3N_4O$	15.5	15.1

*All the compounds were crystallized from aqueous ethanol.
MS: (VIC_1): $M^{+\cdot}$, m/z 336. Calc. mol. wt 336.
(VIC_2): $M^{+\cdot}$, m/z 366. Calc. mol. wt 366.

instrument using TMS as internal standard (chemical shifts in δ, ppm), and the mass spectra at 70 eV on an MS-12 mass spectrometer.

Typical procedures for the preparation of 3-amino-4,5-dihydro-1*H*-pyrazoles and 3-trifluoroacetylamino-4,5-dihydro-1*H*-pyrazoles are given below:

3-Amino-1-(6-methoxy-4-methyl-2-quinolyl)-4,5-dihydro-1H-pyrazole (IIC_2, $R_1 = OCH_3$)

Sodium (0.11 g, 0.0047 mole) was added to abs. ethanol (10 ml) and allowed to react till all the sodium had dissolved. 2-Hydrazino-6-methoxy-4-methylquinoline (2.03 g, 0.01 mole) and acrylonitrile (0.53 g, 0.01 mole) were added and the reaction mixture was heated to reflux for 8 hr. After cooling, the reaction mixture was rendered acidic by the addition of hydrochloric acid. The solid, thus obtained, was filtered and washed with water. It was suspended in dilute ammonia solution, stirred, filtered, washed with water, dried and crystallized from benzene-pet. ether, m.p. 228-30°, yield 1.8 g (70%); IR: 3400, 3320, 3200 (NH), 1640 (C=N, NH bend.); PMR(DMSO-d_6): 2.55 (s, 3H, CH_3), 2.85 (t, 2H, pyrazole CH_2 at position-4), 3.8 (s, 3H, OCH_3) 4.2 (t, 2H, pyrazole CH_2 at position-5), 5.85 (s, 2H, NH_2), 7.0-7.7 (m, 4H, Ar–H); MS: m/z 256 ($M^{+\cdot}$). Calc. mol. wt 256 (Found: C, 65.6; H, 6.5; N, 21.7. $C_{14}H_{16}N_4O$ requires C, 65.6; H, 6.3; N, 21.9%).

Other 3-amino-4,5-dihydro-1*H*-pyrazoles were similarly prepared. Their characterization and analytical data are given in Tables 1, 2 and 3.

3-Trifluoroacetylamino-1-(6-methoxy-4-methyl-2-quinolyl)-4,5-dihydro-1H-pyrazole (VC_2, $R_1 = OCH_3$)

Trifluoroacetic anhydride (3.15 g, 0.015 mole) was added to a solution of 3-amino-1-(6-methoxy-4-methyl-2-quinolyl)-4,5-dihydro-1*H*-pyrazole (2.56 g, 0.01 mole) in dry benzene (20 ml) in the cold and the reaction mixture heated to reflux for 2 hr with occasional shaking. After cooling, the separated solid was collected by filtration, washed with water, dried and crystallized from aq. ethanol, m.p. 140°, yield 2.2 g (62%); IR(nujol): 3400, 3200 (NH), 1660 (C=O), 1620 (C=N, NH bend), 1200, 1180, 1140 (CF_3); PMR(DMSO-d_6): 2.5 (s, 3H, CH_3), 2.8 (t, 2H, pyrazole CH_2 at position-4), 3.8 (s, 3H, OCH_3), 4.25 (t, 2H, pyrazole CH_2 at position-5), 7.1-7.7 (m, 4H, Ar–H) (NH proton could not be located) (Found: N, 15.9. $C_{16}H_{15}F_3N_4O_2$ requires N, 15.9%).

Other 3-trifluoroacetylamino-4,5-dihydro-1*H*-pyrazoles of this series were prepared in a similar manner. Their characterization and analytical data are given in Tables 4 and 5.

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Notes

Synthesis of thiobenzamides by a Willgerodt-Kindler type reaction using benzyl chlorides and secondary amines

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Benzyl chlorides, variously substituted at *p*-position react with secondary amine and sulphur under relatively mild reaction conditions to afford N,N-disubstituted thiobenzamides in moderate to good yields.

Willgerodt-Kindler reaction[1,2] has been used successfully for the synthesis of N,N-disubstituted thioamides from a variety of substrates, e.g. aldehydes, ketones, styrenes, phenylacetylene, benzylmercaptol, ethers etc. The method is simple, and consists of heating a mixture of the substrate, secondary amine, and sulphur. In spite of its versatile nature, no clear-cut mechanism is known as yet[2]. The most common use of the reaction, however, is in the preparation of arylacetic acids from aryl methyl ketones where the intermediate N,N-disubstituted thioamides are hydrolysed directly without isolation. Modified procedures[3,4] have recently been developed using lead tetraacetate and thallium trinitrate with better yields.

In view of certain medicinal (such as choleretic[5]) properties of N,N-disubstituted benzamides and of their extensive use as substrates for the study of restricted rotation[6], we were interested to develop a clean method for their synthesis by the application of Willgerodt-Kindler reaction from easily available starting materials. We report that benzyl chlorides ($ArCH_2Cl$), variously substituted in the *para* position, react with a secondary amines (NHR_2) and sulphur under relatively mild condition to afford N,N-disubstituted thiobenzamides, $Ar\,CSNR_2$ (**2**) in moderate to good yields.

The reaction proceeds presumably through the intermediacy of the tertiary amine, $ArCH_2NR_2$ (**1**). The methylene carbon positioned between two negative groups in **1**, undergoes sulphurisation to give the thiobenzamides (**2**). An isolated example of the reaction of a benzylamine with sulphur giving phenylthiocarbamide is known in the literature[7].

In the present experiments, simple and substituted benzyl chlorides were allowed to react with diethylamine, pyrrolidine and morpholine under identical reaction conditions (heating with sulphur) to give the corresponding N,N-disubstituted benzothiocarbamides in comparative yields (Table 1). The products were identified by spectral properties as well as by comparison with authentic samples prepared by standard methods[6a,8]. The separation in most cases present no special problem and the yields are based on the isolated crystalline products.

Table 1—Reaction conditions and product characteristic data in reaction of benzyl chlorides with secondary amines and sulphur

Chloride	Base	Time of reflux (hr)	Product (% yield)	m.p. °C
Benzyl	Morpholine	3	40	139
Anisyl	Do	7	45	104
Piperonyl	Do	10	18[b]	158
p-Chlorobenzyl	Do	5	62	199
p-Nitrobenzyl	Do	3[c]	60	142
Benzyl	Pyrrolidine	5	70	75
Anisyl	Do	5	94	114
Piperonyl	Do	12	20[b]	126
p-Chlorobenzyl	Do	5	89	102
p-Nitrobenzyl	Do	15 min[c]	93	153
Benzyl	Diethylamine[a]	5	45	42
Anisyl	Do[a]	12	50	45
Piperonyl	Do[a]	10	20[b]	92
p-Chlorobenzyl	Do[a]	5	55	69
p-Nitrobenzyl	Do[a]	3[c]	60	130

(a)Pyridine used as a co-solvent; (b)after chromatographic purification; and (c)stirred at room temperature.

The data in Table 1 show the following features : (i) among the three secondary amines used, pyrrolidine appears to give the best result and morpholine the worst; (ii) benzyl chlorides having a methoxyl, chloro or nitro group in the *para* position give consistently higher yields in comparison to unsubstituted ones; and (iii) *p*-nitrobenzyl chloride requires much milder condition (room temperature) for the reaction and leads to appreciably higher yield with lesser amount of tar formation.

Experimental

General procedure

Powdered sulphur (2.2 g atom) was added to a mixture of benzyl chloride (1 mole) and a large excess of the secondary amine. In the case of die thylamine, pyridine was used as a co-solvent. The

mixture was refluxed (or stirred at room temperature for nitro compounds) with TLC monitoring (disappearance of the benzyl chloride). The usually black tarry mass was poured into ice-water, extracted with ether followed by benzene, and the combined extract was washed repeatedly with aq hydrochloric acid and water. The residue after the removal of solvent was taken up in hot methanol and filtered to remove any unreacted sulfur. The thiobenzamides, crystallised from aq methanol, gave satisfactory elemental analyses and expected IR, mass and ^{1}H NMR spectra. In a few cases, the samples were purified by column chromatography.

The reactions of N,N-diethylbenzylamine, benzylpyrrolidine, and benzylmorpholine were carried out under identical condition by refluxing with sulphur with an excess of the respective secondary amines and pyridine in the case of N,N-diethylbenzylamine.

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1,2-Secopyrethroids: Synthesis of (±) α-(*RS*)-cyano-3-phenoxybenzyl-4-methyl-3-phenyl/*p*-substituted-phenylpentanoates†

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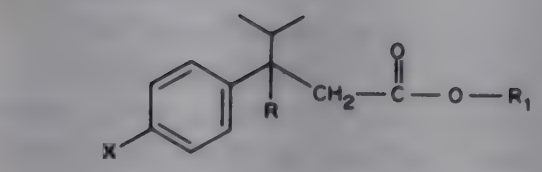
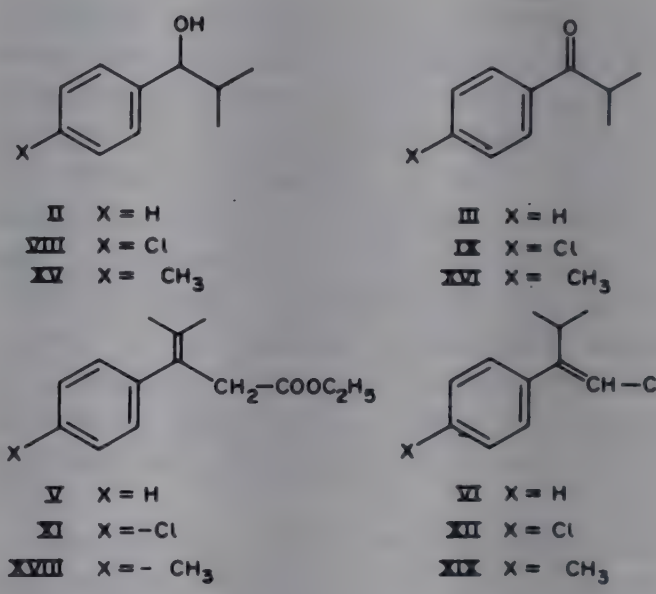
A simple, elegant synthesis of (±) α-(*RS*)-cyano-3-phenoxybenzyl-4-methyl-3-phenyl/*p*-substituted-phenylpentanoates (I, XIV, XXI) has been described.

In a previous communication[1], the synthesis of 3-phenoxybenzyl 3-alkyl-3-phenyl/*p*-substituted-phenylpropionates, bearing structural resemblance with 1,2-secopyrethroids has been reported. However, 1,2-secopyrethroids possessing an isopropyl group β to carboxylate function could not be synthesised by the route described, as the alkylation of diethyl malonate with 1-bromo-1-phenyl-2-methylpropane failed to give the expected product due to steric factors and highly competing base-induced elimination reactions.

We now report a simple and elegant approach for the synthesis of esters of the type I.



I X = R = H , R_1 = –CH(CN)–O–C$_6$H$_5$
IV X = H , R = OH , R_1 = $-C_2H_5$
VII X = R = H , R_1 = $-C_2H_5$
X X = Cl , R = OH , R_1 = $-C_2H_5$
XIII X = Cl , R = H , R_1 = $-C_2H_5$
XIV X = Cl , R = H , R_1 = –CH(CN)–O–C$_6$H$_5$
XVII X = CH_3 , R = OH , R_1 = $-C_2H_5$
XX X = CH_3 , R = H , R_1 = $-C_2H_5$
XXI X = CH_3 , R = H , R_1 = –CH(CN)–O–C$_6$H$_5$



II X = H
VIII X = Cl
XV X = CH_3

III X = H
IX X = Cl
XVI X = CH_3

V X = H
XI X = –Cl
XVIII X = – CH_3

VI X = H
XII X = Cl
XIX X = CH_3

Experimental

Grignard reaction on benzaldehyde using isopropylmagnesium iodide, followed by Jones' chromic acid oxidation of the resulting alcohol(II) furnished isobutyrophenone(III), $C_{10}H_{20}O$, yield 82%. Reformatsky reaction[2] on III using ethyl bromoacetate gave expected (±)-ethyl 3-hydroxy-4-methyl-3-phenyl-pentanoate(IV), $C_{14}H_{20}O_3$ in 86% yield after purification by chromatography (silica gel). Dehydration of IV ($KHSO_4$ distillation, 130°-140°C bath temp./5 mm) furnished a mixture of two isomers (V and VI), $C_{14}H_{18}O_2$ in almost equal proportions as indicated by GC, IR and PMR signals; IR (neat) cm^{-1}: 1730 (ester carbonyl of V), 1710 (ester carbonyl of VI), 1640 (C = C conjugated with ester carbonyl of VI); NMR ($CDCl_3$, 90 MHz): δ 1.17 (m, isopropyl methyls of VI and ester methyls of V and VI), 1.62 and 1.84 (s each, methyls on the double bond of V), 2.64 (m with 7 line-pattern, allylic methine proton of VI), 3.35 (s, allylic methylene α to ester carbonyl of V), 4.01 (m, ester methylenes of V and VI), 5.9 (s, olefinic proton of conjugated C = C of VI). Similar IR PMR and GC results were obtained for the mixtures of XI, XII and XVIII, XIX.

Catalytic hydrogenation of the mixture of V and VI using 5% Pd/C in ethanol gave ethyl-4-methyl-3-phenylpentanoate(VII), $C_{14}H_{20}O_2$ in a quantitative yield. Saponification (KOH/EtOH, room temperature) of VII gave the corresponding acid which was converted into acid chloride ($SOCl_2$/benzene, reflux). The latter was esterified with α-(*RS*)-cyano-3-phenoxybenzyl alcohol (prepared *in situ* from 3-phenoxybenzaldehyde, NaCN, H_2O) under phase transfer conditions (TEBA) according to reported procedure[3] to yield the title compound (±)α-(*RS*)-cyano-3-phenoxybenzyl-4-methyl-3-phenylpentanoate(I), $C_{26}H_{25}NO_3$, in 90% yield; IR (neat) cm^{-1}:

†NCL Communication No. 4484

1750; PMR ($CDCl_3$; 90 MHz): δ 0.73, 0.92 and 0.98 (6H, d each, J = 7 Hz each, isopropyl methyls of both the diasteremers), 1.88 (1H, m, methine proton of isopropyl group), 2.8 (3H, m, methylene protons α to ester carbonyl and benzylic proton), 6.17 and 6.31 (1H, each s, CH − CN of diastereomers).

Following the analogous procedures, cyano esters XIV and XXI were synthesized from the corresponding ethyl esters XIII and XX.

Esters I, XIV and XXI are the higher homologues of the potent non-cyclopropane pyrethroid fenvalerate with different substitutions in the *p*-position of the aromatic ring. These esters can also be viewed as 1,2-secopyrethroids in which the conventional vinyl function has been replaced by an aromatic ring. The insecticidal and larvicidal properties of these compounds is being looked into.

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Cyanomethylation—A convenient route for thiazine synthesis†

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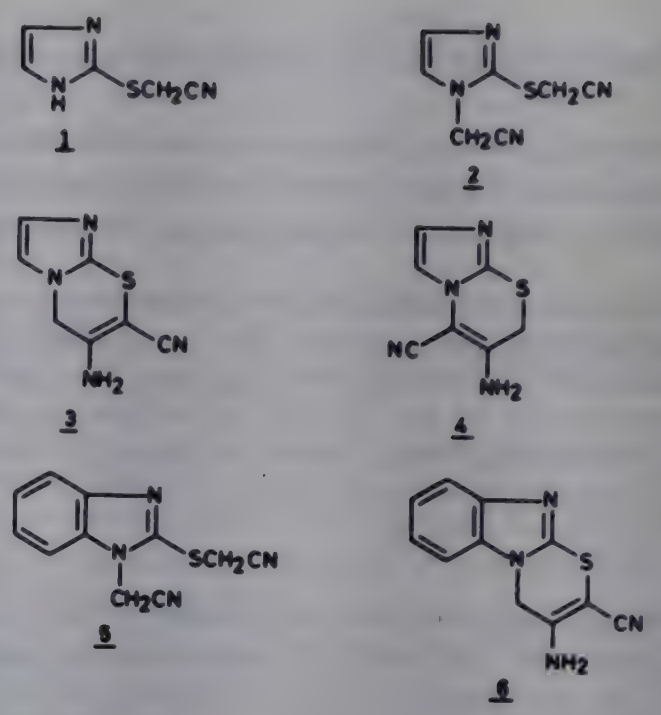
1,2-Dicyanomethyl derivatives of 2-mercaptoimidazole and 2-mercaptobenzimidazole under basic condition are cyclised to condensed 1,3-thiazines (**3**) and (**6**) respectively.

Chloroacetonitrile has been extensively used for cyanomethylation and the presence of cyanomethyl group in appropriate position in a molecule is utilised for building new hetero moieties. In our structure—activity studies cyanomethylation of 2-mercaptoimidazole and 2-mercaptobenzimidazole was conveniently utilised for the synthesis of appropriately substituted imidazothiazine and benzimidazothiazine.

Thus, a mixture of 2-mercaptoimidazole[1] (1 mole) and chloroacetonitrile (2 moles) was refluxed for 1 hr in acetone containing anhydrous potassium carbonate. The reaction mixture on normal work-up afforded a semisolid which on fractional crystallisation from benzene-ethyl acetate afforded 2-cyanomethylthioimidazole (**1**) in quantitative yield, m.p. 151°; IR($CHCl_3$): 2240 cm^{-1} (CN); PMR($CDCl_3$): δ 7.40 (s),7.10(s) for two imidazole protons, 3.9 (s, 2H), methylene ($-SCH_2CN$); MS: m/z 149 [M^+].

Compound **1** on desulphurisation with Raney nickel in ethanol gave imidazole confirming the S-alkylation. When the above reaction was continued for 6 hr in order that both the moles of chloroacetonitrile take part in the reaction, 2-cyanomethylthioimidazole-1-acetonitrile (**2**) as expected was obtained in 80% yield, m.p. 88°; MS: m/z 178 [M^+]; IR($CHCl_3$): 2240 cm^{-1} (CN); PMR($CDCl_3$): δ 7.40, 7.10 for two imidazole protons, 5.20 (s, 2H, $-NCH_2CN$): 3.90 (s, 2H, $-SCH_2CN$). Compound **2** was cyclised by refluxing for 1 hr in sodium methoxide and ethylene glycol dimethylether. The residue after removal of the solvent was diluted with water and the resulting solid was recrystallised from methanol, m.p. 197°; MS: m/z 178 [M^+]; IR(KBr): 3400, 3200 ($-NH_2$), 2180 cm^{-1} (CN); PMR(DMSO-d_6): δ 7.30, 6.90 (two imidazole protons), 4.90 (s, 2H), 2.50 (s, 2H, $-NH_2$ exchangeable with D_2O). The formation of a new compound with same molecular weight as **2** was indicative of intramolecular rearrangement. The presence of two active methylene groups could give either compound **3** or **4** by the attack of methylene on nitrile under basic conditions. Absence of characteristic $-SCH_2$ and presence of $-NCH_2$ signals in PMR confirmed structure **3**, namely 6-amino-7-cyano-5*H*-imidazole[1,2-*b*](1,3)thiazine. **3** was also formed atleast in small yield along with **2** when a mixture of 2-mercaptoimidazole and chloroacetonitrile was refluxed for 10 hr.



Subsequently, 2-cyanomethylthiobenzimidazole-1-acetonitrile (**5**), (m.p. 140° [M^+] 228) was obtained when a mixture of 2-mercaptobenzimidazole[2] (1 mole) and chloroacetonitrile (2 moles) was kept stirred at room temperature for four days in acetone containing anhydrous potassium carbonate. Attempts to increase the rate of above reaction by refluxing resulted in low yields of desired **5**. As in the case of **2** compound **5** was cyclised to 8-amino-9-cyano-7*H*-benzimidazole[1,2-*b*](1,3)thiazine (**6**), m.p. 240° [M^+] 228, under similar conditions. The presence of $-NCH_2$ signal in PMR at δ 4.9 (s, 2H), once again proved the participation of $-SCH_2$ in the cyclisation of **5** to **6**.

One of us (BRR) is thankful to CSIR, New Delhi, for the award of Fellowship.

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†RRL-H Communication No. 2254

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A new synthesis of 3-methylchromones

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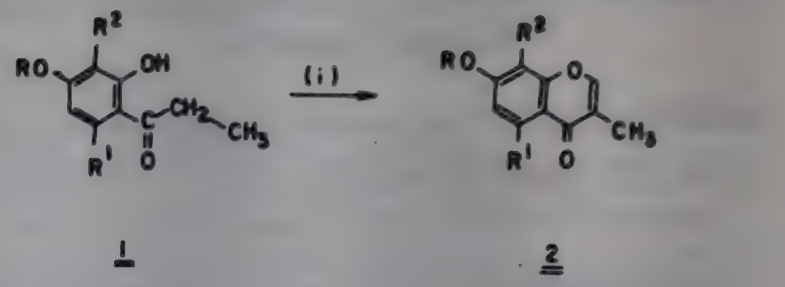
Six chromones (**2a-f**) have been synthesised by treating 2-hydroxypropiophenones (**1a-f**) with DMF, BF_3-etherate and methanesulphonyl chloride. The hydroxy chromones (**2a**, **2c** and **2e**) also on methylation afford the corresponding methyl ethers (**2e**, **2d** and **2f**) identical with those obtained directly from **1**.

3-Methylchromones have been found to be important fungicides[1] and useful as cardiovascular agents or in the treatment of allergy conditions or hyperacidity[2]. Kirkiacharian *et al.*[3] have synthesised these compounds by hydroboration of 3-methyl-4-hydroxycoumarins and subsequent dehydrogenation with Pd/C at 240°. We have now synthesised 3-methylchromones (**2a-f**) by treating 2-hydroxypropiophenones (**1a-f**) with DMF, BF_3 - etherate and methanesulphonyl chloride. These chromones were characterised by their elemental analyses and spectral data. Also 7-hydroxy- (**2a**), 5,7-dihydroxy- (**2c**), and 7,8-dihydroxy- (**2e**)-3-methylchromones were methylated with dimethyl sulphate in the presence of anhyd. K_2CO_3 and acetone. The resultant methyl ethers were found to be identical with those (**2b**, **2d**, **2f**) obtained from **1**.

Experimental

Unless stated otherwise, all melting points are uncorrected; petrol used had the boiling range 60-80°; silica gel was used for column chromatography and TLC; solvent systems used for TLC were: (A) benzene - ethyl acetate (4:1) and (B) benzene - ethyl acetate (3:2); R_f values refer to TLC; UV spectra in methanol were recorded on a Shimadzu 260 spectrophotometer (λ_{max} in nm and figures in parenthesis refer to log ε values); IR spectra were recorded in KBr on a Shimadzu 435 spectrophotometer (ν_{max} in cm^{-1}); and PMR spectra were recorded in $CDCl_3$ on a 90 MHz Perkin-Elmer R-32 spectrometer using TMS as internal standard (chemical shifts in δ, ppm and J values in Hz).



Reaction of 2-hydroxypropiophenones (**1**)with DMF in the presence of BF_3-etherate and methanesulphonyl chloride: Formation of 3-methylchromones (**2**)

To a well-stirred solution of a 2-hydroxypropiophenone (**1a**[4], **1b**[5], **1c**[5], **1d**[6], **1e**[7] or **1f**[8]; 40 mmole) in DMF (25 ml) was added BF_3 - etherate (7 ml) dropwise during 1 hr, and then a solution of methanesulphonyl chloride (4.5 ml) in DMF (10 ml) added to it at 50°. The reaction mixture was heated on a water-bath for 1½ hr, cooled and poured into ice-cold water. The solid that separated was purified by passing through a column using benzene - ethyl (acetate (9:1) as eluant to give **2**. The chromones, thus prepared, were characterized as follows:

7-Hydroxy-3-methylchromone (**2a**): Crystallised from methanol as cream-coloured plates (3.75 g; 59.9%), m.p. 222-24°; R_f 0.45 (solvent A) (Found: C, 67.9; H, 4.7. $C_{10}H_8O_3$ requires C, 68.2; H, 4.5%); UV: 204(4.33), 224(sh) (4.20), 254(4.27), 290(3.85); IR: 3150, 1630, 1540; PMR(CD_3COCD_3): 2.0(s, 3H, CH_3), 6.92(d, J = 2.5 Hz, 1H, H-8), 7.0(dd, J = 2.5 Hz, J = 10 Hz, 1H, H-6), 8.02(s, 1H, H-2), 8.06(d, J = 10 Hz, 1H, H-5).

7-Methoxy-3-methylchromone (**2b**): Crystallised from ethyl acetate - petrol as orange plates (4.32 g; 63.4%), m.p. 113-14° (lit.[3], m.p. 109-10°); R_f 0.66 (solvent A) (Found: C, 69.2; H, 5.4. $C_{11}H_{10}O_3$ requires C, 69.5; H, 5.3%); UV: 238(4.30), 244(sh) (4.26), 272(4.17); IR: 1630, 1600; PMR: 2.0(s, 3H, CH_3), 3.89(s, 3H, OCH_3), 6.79(s, J = 2.5 Hz, 1H, H-8), 6.95(dd, J = 2.5 Hz, J = 10 Hz, 1H, H-6), 7.75(s, 1H, H-2), 8.16(d, J = 10 Hz, 1H, H-5).

5,7-Dihydroxy-3-methylchromone (**2c**): Crystallised from ethanol as cream coloured plates (4.30 g, 62.8%), m.p. 212-13°; gave violet green ferric reaction; R_f 0.67(solvent B) (Found: C, 62.3; H, 4.3. $C_{10}H_8O_4$ requires C, 62.5; H, 4.2%); UV: 226 (4.29), 248(4.36), 255(4.35), 292(4.03); IR: 3300, 2950, 1640, 1580; PMR(CD_3COCD_3): 1.95(s, 3H, CH_3), 6.33(d, J = 2.5 Hz, 1H, H-8), 6.40(d, J = 2.5 Hz, 1H, H-6), 8.03(s, 1H, H-2), 12.74(s, 1H, chelated OH).

5,7-Dimethoxy-3-methylchromone (**2d**): Crystallised from ethyl acetate - petrol as colourless plates (5.16 g; 64.5%), m.p. 101-2°; R_f 0.40(solvent B) (Found: C, 65.2; H, 5.6. $C_{12}H_{12}O_4$ requires C, 65.4; H, 5.4%); UV: 202(4.23), 226(4.27), 250(4.26), 282(3.90); IR: 1650, 1605; PMR: 1.94(s, 3H, CH_3), 3.84 and 3.90(2s, 3H each, 2 × OCH_3), 6.32(bs, 2H, H-6 and H-8), 7.53(s, 1H, H-2).

7,8-Dihydroxy-3-methylchromone(**2e**): Crystallised from ethanol as light brown plates (4.34 g; 62.9%), m.p. 203-04°; R_f 0.74 (solvent A) (Found: C, 62.2; H, 4.3. $C_{10}H_8O_4$ requires C, 62.5; H, 4.2%); UV: 204(4.43), 224(4.35), 254(4.46), 288(4.05); IR: 2850, 1675, 1580; PMR(CD_3OD): 2.02(s, 3H, CH_3), 7.0(d, J = 10 Hz, 1H, H-6), 7.60(d, J = 10 Hz, 1H, H-5), 8.14(s, 1H, H-2).

7,8-Dimethoxy-3-methylchromone (**2f**): Crystallised from ethanol as orange plates (5.23 g; 65.4%), m.p. 131-32°; R_f 0.56(solvent A) (Found: C, 65.2; H, 5.5. $C_{12}H_{12}O_4$ requires C, 65.4; H, 5.4%); UV: 229(4.38), 250(4.33), 296(4.26); IR: 1630, 1600; PMR: 2.02(s, 3H, CH_3), 4.0 and 4.02(2s, 3H each, 2 × OCH_3), 7.11(d, J = 10 Hz, 1H, H-6), 7.93(s, 1H, H-2), 7.96(d, J = 10 Hz, 1H, H-5).

Methylation of hydroxy 3-methylchromones

To a solution of the hydroxy 3-methylchromone (**2a**, **2c** or **2e**) (10 mmole) in dry acetone (25 ml) were added dimethyl sulphate [1.1 ml (11 mmole) for **2a**, and 2.2 ml (22 mmole) for **2c** and **2e**] and dry potassium carbonate (5.56 g, 40 mmole) and the resulting (mixture was refluxed for 6 hr. The products after work-up were characterised and found to be identical with the corresponding methyl ethers (**2b**, **2d** and **2f**) obtained above.

Acknowledgement

The authors express their gratitude to CSIR, New Delhi for the award of a senior research fellowship to one of them (O D T).

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Synthesis of 2,3-dihydro-5,7-dihydroxy-6,8-di(3-methyl-2-butenyl)-2-(2-hydroxy-4-methoxyphenyl)-4*H*-1-benzopyran-4-one

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The synthesis of the title compound (VI) has been achieved starting from 2′-hydroxy-4-methoxy-2, 4′,6′-tri(methoxymethoxy)chalcone (III). Treatment of III with prenyl bromide in the presence of methanolic KOH affords 2′-hydroxy-4-methoxy-2, 4′, 6′-tri(methoxymethoxy)-3′, 5′-di(3-methyl-2-butenyl)chalcone (IV) which on cyclization followed by demethoxymethylation furnishes VI.

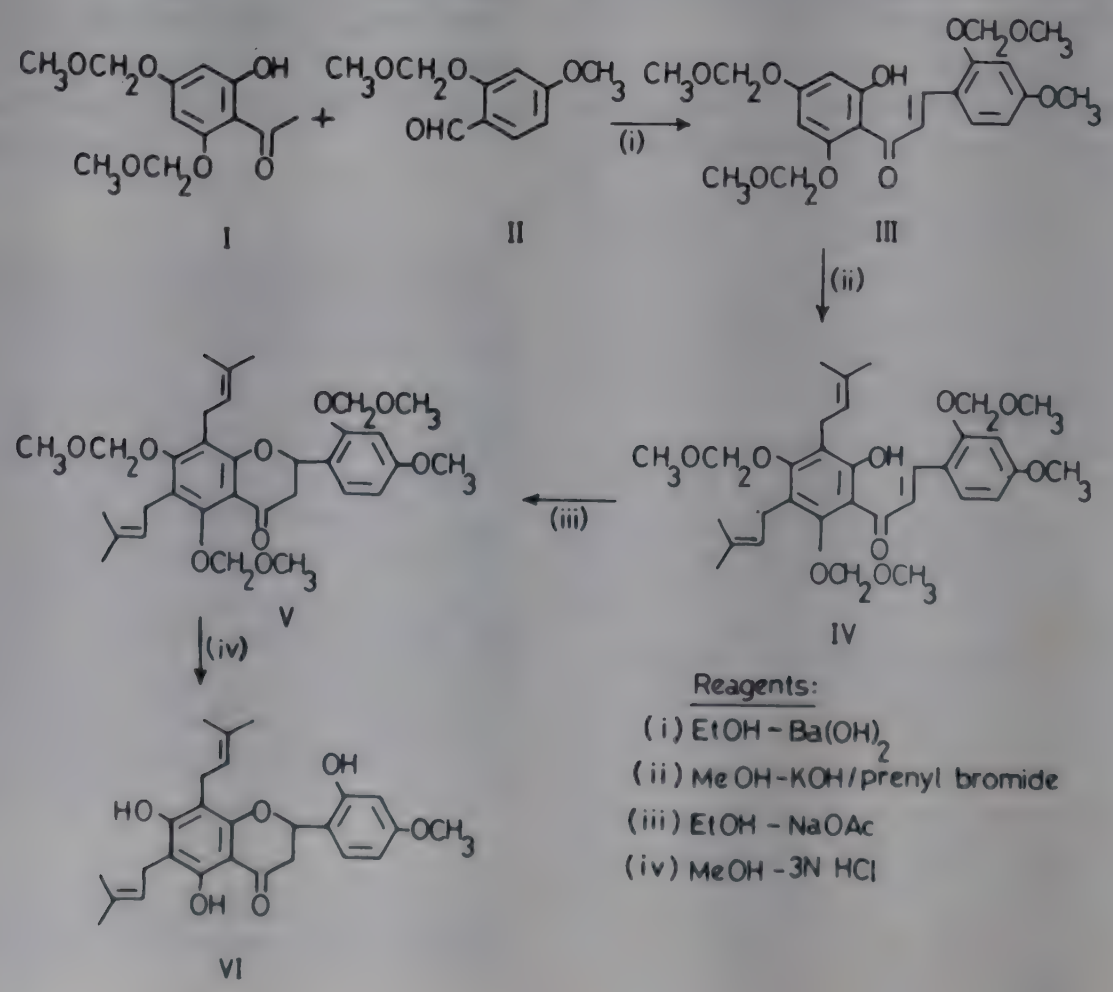
In a recent paper, Wang *et al.*[1] have reported the isolation of 6,8-di(γ,γ-dimethylallyl)-4′-methoxy-5, 7, 2′-trihydroxyflavanone(lespedezaflavanone-A; VI) from the root bark of *Lespedeza davidii*. The isolation of a flavanone with the same structure from the roots of *Flemingia stricta* Roxb. has been reported earlier by Rao *et al.*[2] who gave the name flemiflavanone-A to it. The structure was deduced on the basis of physical and spectroscopic evidences. We report herein the synthesis of a flavanone corresponding to the above structure (VI).

The synthesis of VI was achieved starting from 2′-hydroxy-4-methoxy-2, 4′, 6′-tri(methoxymethoxy)chalcone (III), which was prepared by condensation of 2-hydroxy-4,6-di(methoxymethoxy)acetophenone[3] (I) with 4-methoxy-2-methoxymethoxybenzaldehyde (II). Prenylation of III with prenyl bromide in the presence of methanolic KOH furnished 2′-hydroxy-4-methoxy-2, 4′, 6′-tri(methoxymethoxy)3′, 5′-di(γ, γ-dimethylallyl)chalcone (IV). Cyclization of IV with ethanolic sodium acetate afforded V which on demethoxymethylation using methanolic HCl gave the title compound (VI). The synthetic sample was fully characterized by its melting point[1] and spectroscopic data (UV, IR, PMR).

The salient feature of this synthesis is the preparation of the chalcone III in a better yield using activated barium hydroxide[4] and refluxing for only 1-2 hr.

Experimental

Unless stated otherwise, all m.ps are uncorrected. UV spectra were recorded in methanol on a Shimadzu UV-VIS-260 spectrophotometer, IR spectra in KBr or nujol on a Shimadzu IR-435 spectropho-



tometer and PMR spectra in $CDCl_3$ on a Perkin-Elmer R-32 (90 MHz) or a Jeol FX-100 (100 MHz) FT instrument using TMS as internal standard.

4-Methoxy-2-methoxymethoxybenzaldehyde (II)

A mixture of 2-hydroxy-4-methoxybenzaldehyde (4.0 ml), dry acetone (150 ml), anhyd. potassium carbonate (10.0 g) and methoxymethyl chloride (2.8 ml) was refluxed for 10-15 min and the reaction mixture worked up as usual to give the product as a light brown solid (3.5 g; 87.5%), m.p. 157° (Found: C, 61.3; H, 6.0. $C_{10}H_{12}O_4$ requires C, 61.2; H, 6.1%); UV: 206, 232, 268 nm; IR: 1660, 1620, 1510 cm^{-1}; PMR: δ 3.40 (s, 3H, OCH_2OCH_3), 3.85 (s, 3H, OCH_3), 5.13 (s, 2H, OCH_2OCH_3), 6.50-6.58 (dd, 2H, J = 8.5 Hz and J = 2.5 Hz, H-3 signal merged with H-5 doublet), 7.60 (d, 1H, J = 8.5 Hz, H-6) and 10.20 (s, 1H, CHO).

2′-Hydroxy-4-methoxy-2,4′,6′-tri(methoxymethoxy)-chalcone (III)

A mixture of 2-hydroxy-4, 6-di(methoxymethoxy)acetophenone (I; 2.0 g, 40 mmole) and 4-methoxy-2-methoxymethoxybenzaldehyde (II; 1.54 g, 40 mmole) in ethanol (75 ml) containing activated barium hydroxide (1.0 g, 4.0 mmole) was refluxed for 1-2 hr. The reaction mixture was poured over crushed ice and acidified with dil. HCl. The product was isolated and purified by column chromatography using pet. ether-acetone (24 : 1) as eluant. It crystallized from ethanol as yellow needles (2.0 g, 80%), m.p. 66-67° (Found: C, 60.6; H, 6.0. $C_{22}H_{26}O_9$ requires C, 60.8; H, 5.9%); UV: 205, 279, 364 nm; IR: 3100, 1660, 1600, 1510, 1380 cm^{-1}; PMR: δ 3.48 (s, 9H, $3\times OCH_2OCH_3$), 3.90 (s, 3H, OCH_3), 5.12 (s, 2H, OCH_2OCH_3), 5.20 (s, 4H, $2\times OCH_2OCH_3$), 6.28 (d, 2H, J = 3.0 Hz, H-3′ and H-5′), 6.44 (d, 1H, J = 10.0 Hz, H-β), 6.52-6.64 (dd, 2H, J = 8.5 Hz and J = 2.5 Hz, H-3 and H-5), 7.46 (d, 1H, J = 8.5 Hz, H-6), 8.02 (d, 1H, J = 10.0 Hz, H-α) and 12.68 (s, 1H, chelated −OH).

2′-Hydroxy-4-methoxy-2, 4′, 6′-tri(methoxymethoxy)-3′, 5′-di(3-methyl-2-butenyl)chalcone (IV)

The chalcone III (1.8 g) was added to a well cooled solution of KOH (3.0 g) in abs. methanol (30 ml) and the whole solution cooled to 0°. Prenyl bromide (3.5 ml) was then added dropwise with continuous stirring and the reaction mixture stirred at room temperature for 3-4 hr. The product after usual work-up was subjected to column chromatography over silica-gel. The prenylated chalcone eluted with pet. ether-acetone (47 : 3) as a dark yellow liquid, was crystallized from hot ethanol as yellow needles (200 mg, 17%), m.p. 110° (Found: C, 67.2; H, 7.4. $C_{32}H_{42}O_9$ requires C, 67.4; H, 7.4%); UV: 206, 232, 310 and 384 nm; IR: 3100, 1650, 1610, 1500, 1360 cm^{-1}, PMR: δ 1.64, 1.68, 1.74, 1.79 (4s, 12H, $4\times -CH_3$), 3.30-3.44 (two overlapping doublets, 4H, $2\times Ar-CH_2-$), 3.50 (s, 9H, $3\times OCH_2OCH_3$), 3.90 (s, 3H, OCH_3), 5.00 (s, 2H, OCH_2OCH_3), 5.15 (m, 2H, $2\times -CH_2-CH=$), 5.22 (s, 4H, $2\times OCH_2OCH_3$), 6.40 (d, 1H, J = 10.0 Hz, H-β), 6.57-6.68 (dd, 2H, J = 8.5 Hz and J = 2.5 Hz, H-3 and H-5), 7.46 (d, 1H, J = 8.5 Hz, H-6), 7.94 (d, 1H, J = 10.0 Hz, H-α) and 12.42 (s, 1H, chelated −OH).

4′-Methoxy-2′, 5, 7-tri(methoxymethoxy)-6,8-di(3-methyl-2-butenyl)flavanone (V)

Sodium acetate (2.0 g) was added to IV (150 mg) in ethanol (20 ml) and the mixture maintained at 60-70° for 3-4 hr and then left at room temperature for three days. The product which was a mixture of the chalcone and flavanone was subjected to column chromatography over silica gel. The flavanone was obtained as yellow liquid on elution with pet. ether-acetone (21 : 4), yield 50 mg (34%) (Found: C, 67.5; H, 7.2. $C_{32}H_{42}O_9$ requires C, 67.4; H, 7.4%); UV: 206, 244, 274 nm; IR: 1660, 1610, 1500, 1380 cm^{-1}; PMR: δ 1.65, 1.68, 1.72, 1.74 (4s, 12H, $4\times -CH_3$), 2.92 (dd, 2H, C_3-H), 3.30, 3.38 (2d, 4H, J = 7.0 Hz, $2\times Ar-CH_2-$), 3.48 (s, 9H, $3\times OCH_2OCH_3$), 3.90 (s, 3H, OCH_3), 4.98 (s, 2H, OCH_2OCH_3), 5.15 (m, 2H, $2\times -CH_2-CH=$), 5.22 (s, 4H, $2\times OCH_2OCH_3$), 5.48 (dd, 1H, J = 13.0 Hz and J = 3.0 Hz, C_2-H), 6.50-6.58 (dd, 2H, J = 8.5 Hz and J = 2.5 Hz, H-3′ and H-5′), 7.38 (d, 1H, J = 8.5 Hz, H-6′).

2′, 5, 7-Trihydroxy-4′-methoxy-6, 8-di-(3-methyl-2-butenyl)flavanone (VI)

To a solution of V (25 mg) in methanol (4.0 ml) was added 3*N* hydrochloric acid (4.0 ml) and the reaction mixture boiled for 5-10 min. Ice-cold water was then added and the solution extracted with ether. The organic layer was washed with water, dried (Na_2SO_4) and concentrated. The flavanone was obtained as bright yellow needles (12 mg, 48%) m.p. 154-55° (lit.[1], m.p. 157-58°) (Found: C, 71.2; H, 6.7. Calc. for $C_{26}H_{30}O_6$: C, 71.2; H, 6.9%); UV: 206, 275, 360 nm; IR: 3200, 1640, 1510, 1380 cm^{-1}; PMR: δ 1.68, 1.72, 1.74, 1.76 (4s, 12H, $4\times -CH_3$), 2.90 (dd, 2H, C_3-H), 3.32, 3.38 (2d, 4H, J = 7.0 Hz, $2\times Ar-CH_2-$), 3.90 (s, 3H, OCH_3), 5.18 (m, 2H, $2\times -CH_2-CH=$), 5.50 (dd, 1H, J = 13.0 Hz and J = 3.0 Hz, C_2-H), 6.25, 6.38 (2s, 2H, $2\times OH$), 6.50-6.58 (dd, 2H, J = 8.5 Hz and

J = 2.5 Hz, H-3′ and H-5′), 7.25 (d, 1H, J = 8.5 Hz, H-6′) and 12.45 (s, 1H, C_5-OH).

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Reduction of 3β-chloro-6-nitrocholest-5-ene with Raney nickel - hydrazine hydrate : A synthesis of dimers

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Treatment of 3β-chloro-6-nitrocholest-5-ene (I) with Raney nickel-hydrazine hydrate affords 3β,3β-dichloro-5α,5′α-6,6′-bis-azocholestane (III) and 3α,5α:3′α,5′α-dicyclo-6,6′-bis-azocholestane (IV) along with 3β-chlorocholestan-6-one (II).

Nitroolefins are immensely used as intermediates in organic synthesis and several methods are known to convert them into carbonyl, amino, oxime and aldehydic compounds[1–7]. The reaction of nitroolefins with Raney nickel and sodium hyposulphate gives the corresponding ketones[8]. Herein we wish to report an unexpected dimerization of 3β-chloro-6-nitrocholest-5-ene (I) on treatment with Raney nickel and hydrazine hydrate. The present study is in continuation of our work on the reactions of steroids[9–11].

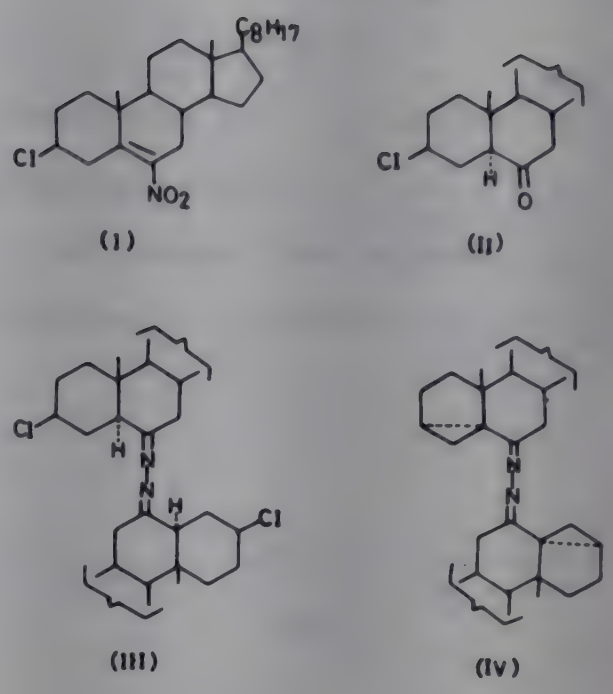
3β-Chloro-6-nitrocholest-5-ene (I) was treated with hydrazine hydrate - Raney nickel, when three crystalline compounds (m.ps 129°, 171° and 207°) were obtained.

The compound having m.p. 171° analysed for $C_{54}H_{90}N_2Cl_2$ which was further supported by the molecular ion peaks at m/z 834, 836 and 838 in its mass spectrum. Its IR spectrum showed bands at 1625 (C_6=N-N=$C_{6'}$) and 720 cm^{-1} (C_3-Cl, $C_{3'}$-Cl). The PMR spectrum exhibited a multiplet centred at δ 3-7 which was assigned to $C_3\alpha$-H and $C_{3'}\alpha$-H ($W_{\frac{1}{2}}$ = 17Hz; axial).

The compound having m.p. 207° analysed for $C_{54}H_{88}N_2$ ($M^{+\cdot}$ 764). Its IR spectrum displayed bands at 3030(cyclopropane ring system) and 1625cm^{-1}(C_6=N-N=$C_{6'}$). The PMR spectrum was featureless except for the signals at δ 0.5-0.65 due to cyclopropane ring protons.

Experimental

Melting points were determined on a Kolfer's block and are uncorrected. Pet. ether refers to the fraction with b.p. 60-80°. Angular and side chain methyl protons appeared in the range δ 1.20-0.70 in the PMR spectra.



Treatment of 3β-chloro-6-nitrocholest-5-ene (I) with hydrazinehydrate and Raney nickel

3β-Chloro-6-nitrocholest-5-ene (I, 3g) in ethanol (100 ml) was treated with hydrazinehydrate (5ml) in the presence of Raney nickel (0.75 g) at room temperature. After the reaction was over, the reaction mixture was filtered and the filtrate diluted with water and extracted with ether. The ethereal layer was washed successively with water, sodium hydrogen carbonate solution (5%) and water, dried (anhyd. sodium sulphate), solvent removed and the residue chromatographed over silica gel (60g). Elution with pet. ether - ether (20:1) afforded 3β-chloro-5α-cholestan-6-one (II) which was recrystallized from methanol, yield, 100 mg, m.p. 129°(lit.[13], m.p. 129-30°) (Found:C, 77.2; H, 10.7. $C_{27}H_{45}OCl$ requires C, 77.1; H, 10.7%); IR(KBr) 1700 (C=O), 750cm^{-1} (C-Cl); PMR ($CDCl_3$): δ 3.7 (1H, m, $C_3\alpha$-H; $W_{\frac{1}{2}}$ = 18Hz).

Further elution with pet. ether - ether (15:1) gave an oil (III) which crystallized from methanol, yield, 900 mg, m.p. 171° (Found : C, 77.5; H, 10.7; N, 3.4. $C_{54}H_{90}N_2Cl$ requires C, 77.5; H, 10.8; N, 3.4%); IR(KBr) : 1625 (C_6=N−N=$C_{6'}$) and 720cm^{-1} (C_3-Cl and $C_{3'}$-Cl); PMR($CDCl_3$) : δ 3.7(2H, m, $C_3\alpha$-H and $C_{3'}\alpha$-H; $W_{\frac{1}{2}}$ = 17Hz); MS : m/z 834($M^{+\cdot}$), 836(P+2), 834(P+4).

Continued elution with pet. ether - ether (13:1) provided the compound IV, which recrystallized from methanol, yield 700 mg, m.p. 207°(Found : C, 84.9; H, 11.5; N, 3.6. $C_{54}H_{88}N_2$ requires C, 84.8; H,

11.5; N, 3.7 %); IR(KBr) : 3030(cyclopropane ring) and 1625cm^{-1} (C_6=N-N=$C_{6'}$); PMR ($CDCl_3$) : δ 0.5 - 0.65 (complex signal, cyclopropane ring protons); MS : m/z 764 ($M^{+\cdot}$).

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Reaction of dimethyloxosulphonium-methylide with oxaziridines—Transformation to azetidines

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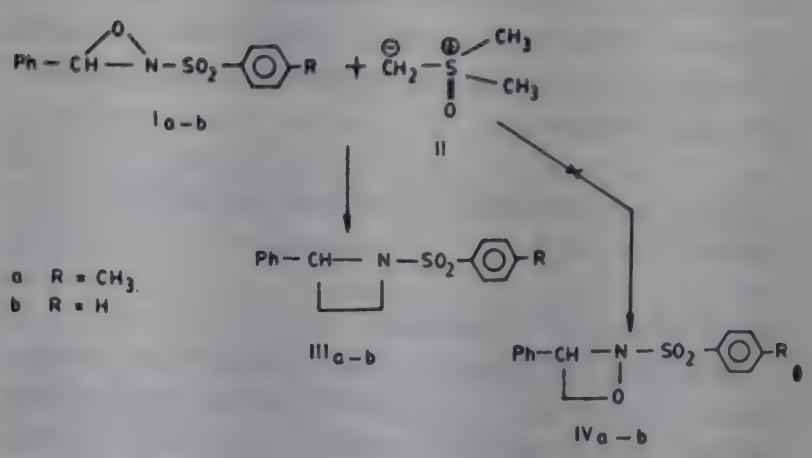
Reaction of N-arylsulphonyloxaziridines with dimethyloxosulphoniummethylide yields azetidines whereas a similar reaction with N-alkyloxaziridines leads to the corresponding azomethines.

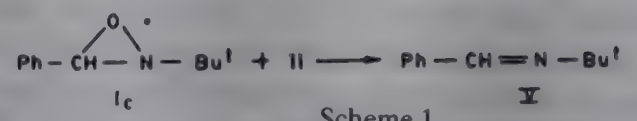
Methylene transfer from sulphur ylides to double bonds has been used often to prepare three-membered heterocycles and carbocycles[1-3]. However, with the exception of Carrie *et al.*[4], further reactions of these three-membered rings with sulphur ylides have not received much attention. Sometime back it was reported from our laboratory that methylene transfer to aziridine was quite general and constituted a fairly simple route to azetidines[5,6]. While we were working along similar lines to synthesise other four-membered rings, Okuma *et al.*[7] showed the feasibility of this approach for obtaining oxetanes. We report herein, for the first time, results of reactions of dimethyloxosulphoniummethylide with some oxaziridines as an approach to oxazetidines, which are not easily accessible otherwise.

Oxaziridines (Ia, b) were prepared by MCPBA oxidation of the corresponding azomethine as described previously[8]. Ic was synthesised through Emmon's procedure[9]. Reaction of Ia, b (1 equiv) with dimethyloxosulphoniummethylide (II, 4 equiv) in dry THF and under N_2 atmosphere at room temperature for 18 hrs resulted in a complex mixture. Chromatography on neutral alumina gave the pure azetidines (IIIa, b) in 36-38% yield (see Experimental). No other product could be isolated and surprisingly none of the expected oxazetidines (IVa, b) could be obtained.

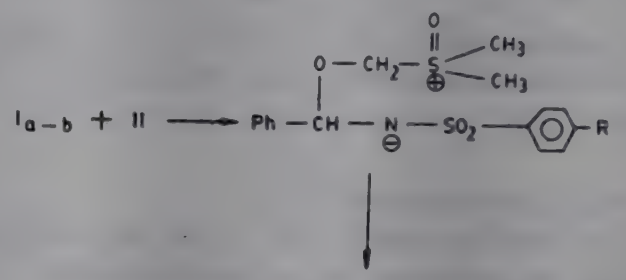
In contrast to behaviour of Ia, b, the oxaziridine (Ic) under these conditions underwent deoxygenation to the corresponding azomethine (V) (see Scheme 1). These results have been rationalised on the basis of results obtained by us earlier[5,6,10] (see Scheme 2).

In support of the two consecutive methylene transfer reactions, is the fact that treatment of oxaziridines with lesser amount of the ylide (2 equiv) led to isolation of the corresponding aziridine. In the case of oxaziridine (Ic) the azomethine was isolable because it was unreactive towards II. In fact, reaction of V with II, in a separate experiment, proved abortive and V could be recovered unchanged nearly quantitatively.





Scheme 1



Scheme 2

Experimental

Melting points are uncorrected. IR spectra were recorded on a Pye-Unicam SP-1200 grating spectrophotometer, ^1H and ^{13}C NMR on a JEOL FX-100 machine and mass spectra (70 eV) on a JMS D300 (JEOL) GC/MS spectrometer.

Reaction of oxaziridines (I) with dimethyloxosulphoniummethylide (II): General procedure

The ylide (II) was prepared from appropriate amounts of trimethyloxosulphonium chloride and sodium hydride as reported[2]. To the room temperature solution of the ylide, a THF solution of the oxaziridine was added under N_2 blanket and stirred for 18 hr. The reaction mixture was diluted with water

and extracted with ether (5 × 30 ml). The combined ethereal extract was washed with water (3 × 30 ml), dried and stripped of the solvent. The residue was subjected to column chromatography using neutral alumina. The azetidines and/or aziridines were eluted with benzene and recrystallised from benzene-pet. ether mixture.

Reaction of 3-phenyl-2-(p-toluenesulphonyl)-oxaziridine (Ia)

(*a*) *With 4 equivalents of II*

The ylide (II) obtained from trimethyloxosulphonium chloride (0.938 g, 0.0073 mole) and sodium hydride (0.350 g, 0.0073 mole) in dry THF (15 ml) was treated with Ia[8] (0.5 g, 0.0018 mole) and after the reaction was over (18 hr), the mixture was worked-up as described under the general procedure. Elution with benzene gave azetidine (IIIa) as a crystalline solid (0.2 g, 38.3%), m.p. 118-19°; IR 1350, 1140 cm^{-1} (νSO_2); PMR ($CDCl_3$): 87.5 (m, 9H, aromatic), 4.9 (t, 1H, J = 8 Hz), 3.78 (t, 2H, J = 8 Hz), 2.28 (m, 2H), 2.44 (s, 3H); MS: m/z 287 (M^+) (Found: C, 66.7; H, 6.1. Calc: C, 66.9; H, 5.9%).

(*b*) *With 2 equivalents of II*

In the reaction which took 15 hr for completion aziridine was obtained as a crystalline solid (0.15 g, 60.4%), m.p. 87-89° (lit.[11] m.p. 88-89°).

Reaction of 3-phenyl-2-benzenesulphonyloxaziridine Ib with 4 equivalents of II

In the reaction, which took 18 hr for completion, azetidine (IIIb) was obtained as a crystalline solid (0.190 g, 36.2%), m.p. 124-25°C (lit.[12] m.p. 123-24°C).

Reaction of 3-phenyl-2-t-butyloxaziridine (Ic) with 4 equivalents of II

In the reaction which took 18 hr for completion, azomethine (V) was obtained (1.59 g, 87%), which was identical (IR, TLC) with an authentic sample of V.

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Action of boron trifluoride etherate and stannic chloride on heterocyclic aromatic acetals

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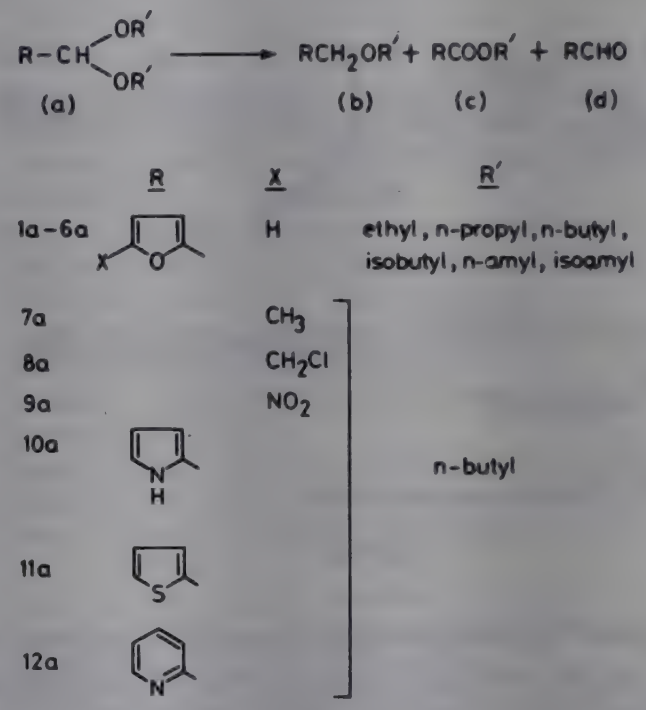
Twelve heterocyclic aromatic acetals (**1a-12a**) have been synthesised and their reactions with Lewis acids, viz. boron trifluoride etherate (BTE) and stannic chloride (STC) have been studied. The acetals yield ethers, esters and aldehydes with BTE, but only esters and aldehydes with STC. Interestingly, pyridine-2-aldehyde acetal (**12a**), yields aldehyde alone, that too in low yield. Probable mechanisms have been suggested for the product formation.

The reactions of heterocyclic aromatic acetals catalyzed by Lewis acids, in contrast to those of aromatic homocyclic and aliphatic acetals[1–3], have received only scanty attention. Aliphatic acetals give ether-alcohols as the major products, while aromatic homocyclic acetals yield esters and ethers as the main products. This feature induced the authors to take up the title investigation. Boron trifluoride etherate[4], and stannic chloride[5] are synthetically very useful reagents and vary widely in their Lewis acid character and reactivity. Hence their application in the present work.

Action of boron trifluoride etherate (BTE)

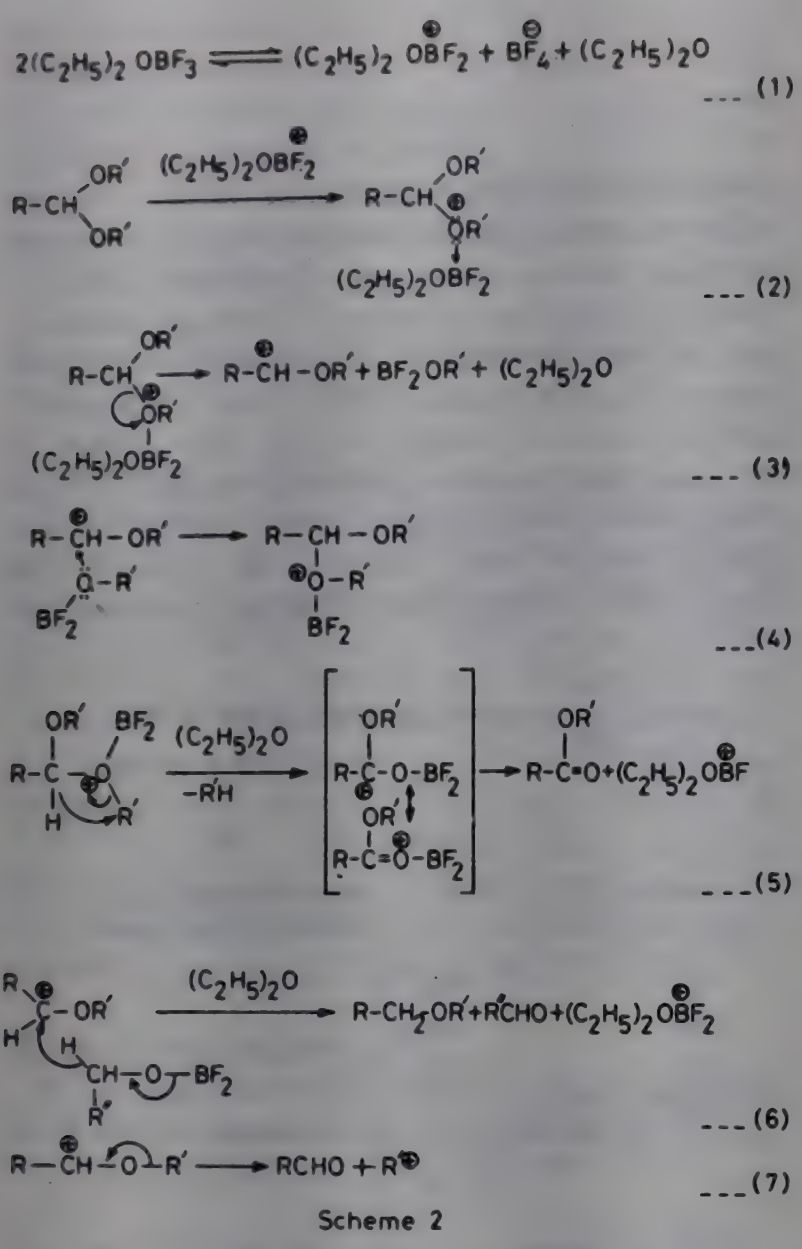
The reactions of acetals with BTE gave the corresponding ethers, esters and aldehydes (Table 1, Scheme 1). Based on evidences[6–8] probable mechanisms are put forward for the products formation (Scheme 2). Dissociation of BTE (step 1) is known[9]. Such a process is favoured by the high stability of BF_4^- and the resultant positively charged species $(C_2H_5)_2OBF_2^+$ would cause greater reactivity[10] than $(C_2H_5)_2OBF_3$. And hence the attack of $(C_2H_5)_2OBF_2^+$ was preferred. Further evidences are



Scheme 1

Table 1—Percentage of products of acetals by the action of $(C_2H_5)_2OBF_3$ and $SnCl_4$

Acetal	Conversion (%)	Ether	Ester	Aldehyde	Conversion (%)	Ester	Aldehyde
	$BF_3O(C_2H_5)_2$ catalysis				$SnCl_4$ catalysis		
1a	100	54	15	19	72	52	48
2a	100	54	13	20	75	54	46
3a	100	57	10	21	76	58	42
4a	100	60	5	26	82	69	31
5a	100	56	9	24	77	60	40
6a	100	58	9	23	81	67	33
7a	100	65	13	8	100	78	22
8a	90	47	8	36	71	39	61
9a	49	—	—	94	34	—	100
10a	100	56	16	17	74	55	45
11a	100	53	15	20	80	59	41
12a	25	—	—	87	17	—	100

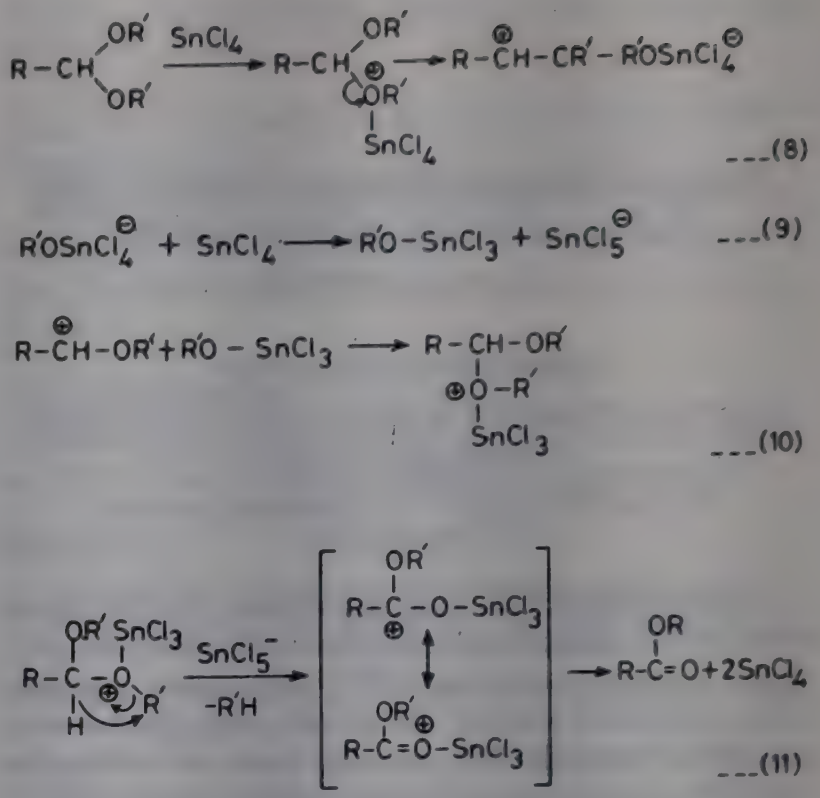


Scheme 2

available[7,8] for the coordination of BTE with the lone pair oxygen leading to bond cleavage producing carbocation (step 3). The carbocation intermediate is considered to follow three different pathways to yield three products: (i) it undergoes nucleophilic attack[12] by BF_2OR' followed by bond cleavage to yield the ester (steps 4,5); (ii) it interacts with BF_2OR' to effect MPV type of reduction, producing ether (step 6) (A number of BTE catalyzed reactions[6,7] reaffirm such hydride shift reduction process. Detection of aliphatic aldehyde of the type R″CHO evidently indicates the possible operation of the mechanism); and (iii) it may also undergo internal cleavage[3], liberating the parent aldehyde and alkyl carbocation (step 7) which may eliminate a proton to yield an olefin. GLC confirms the presence of olefin.

Action of stannic chloride (STC)

In contrast the reaction with STC gave only the ester and aldehyde (Table 1). In accord with the earlier report[2] probable mechanism has been suggested (Scheme 3). The carbocation intermediate on nucleophilic attack by tin alkoxide would produce ester. The remarkable increase in ester yield with the introduc-



Scheme 3

tion of external tin alkoxide into the reaction mixture eloquently suggests the alkoxide coordination during the course of reaction (step 10). The aldehyde results by the step 7 of scheme 2.

The absence of ether formation in STC-catalysed reactions may be ascribed to the failure of hydride reduction[2] course as suggested with BTE catalyzed reaction. But, with STC, nucleophilic attack by the alkoxide seems to be prevalent. The metal atom in tin alkoxide is electropositive in nature and as a result the freely available lone pair on oxygen would acentuate the nucleophilic character of the alkoxide for facile attack. On the other hand, the hydride shift requires bond breaking prior to the attack and this seems to be a high energy process when compared to the nucleophilic attack by the alkoxide where just the lone pair extension occurs.

In BF_2OR', the lone pair availability on oxygen is expected to be much less due to the influence[13] of electron deficient boron supplemented by powerful electronegative fluorine atoms. This accounts for the low yield of esters. In the event of such restrained alkoxide attack, the hydride shift reduction would take the lead resulting in good yield of ether.

A highlight in the study is that as the size of the alkyl group increases, the reaction with BTE gives progressively increased yield of ether while with STC, the yield of the ester increases. In general, coordination of BTE and STC with electron-rich species depends primarily on steric factor[14–16]. As the size of the alkyl group increases, the BF_2OR' would become less stable and as a result the alkoxide once formed may undergo efficient B-O bond cleavage promoting hy-

dride shift leading to good yield of ethers (step 6). In the case of STC the stability of the anion $SnCl_4OR^-$ is expected to depend[2,16] on the size of the alkyl group. The complex anion $(SnCl_4OR)^-$ with a distorted tetrahedral geometry[17,18] would undergo a change faster to produce the required tin alkoxide ($SnCl_3OR'$), when the alkyl group becomes bulkier. This may be the cause for the progressive increase in the yield of ester as we proceed from ethyl to isoamyl.

The acetal (**9a**) having the nitro group in the ring did not yield the desired products – ether and ester – probably due to the fact that the nitro group effectively destabilizes the intermediate carbocation thereby depriving the nucleophilic attack[2,3]; in turn the carbocation undergoes efficient internal cleavage yielding aldehyde. On the contrary the methyl group stabilizes the carbocation and which is reflected in the higher yield of the desired products with acetal (**7a**). Pyridine-2-aldehyde acetal (**12a**) behaved rather anomalously, producing aldehyde alone and that too in poor yield. This may be attributed to the tenacious[19] coordination of the Lewis acid with the lone pair nitrogen of the pyridine nucleus. The generation of the positive charge as a result of such a coordination, destabilizes the incipient carbocation as in the case of nitro substituted acetal. Unlike STC, BTE effected efficient conversions. This emphatically supports the fact that the attacking entity is $(C_2H_5)_2OBF_2^+$ (see ref. 9).

Experimental

PMR spectra were recorded on a Varian HA-100D in $CDCl_3$ using TMS as the internal standard and IR spectra on a Perkin-Elmer 781 spectrophotometer. GLC was performed on a Toshniwal RLO_4 (3mm × 2.5m) column packed with 5% SE-30 on chromosorb W-HP. Column chromatography and TLC were done on silica gel (BDH, Bombay).

Acetals were synthesised by adopting the literature procedures[20,21] and characterized by IR and PMR spectral data. Boron trifluoride etherate (BDH/England) was purified as per the method suggested by Zweifel and Brown[22]. Stannic chloride was prepared by the action of chlorine on commercially available tin and purified by distillation[23].

In a typical experiment, a solution of the acetal (0.1 mol) in purified 1,2-dichloroethane (50 ml) was cooled to 0°C and to this was added freshly purified catalyst (0.1 mol) in 1,2-dichloroethane (50 ml) dropwise during 15 min, under anhydrous conditions. A deep violet colour developed as the addition of the catalyst continued. The reaction was allowed to proceed for another 15 min, quenched by shaking with ice-cold water, washed with 5% aq sodium bicarbonate and water, until the solution became neutral to litmus. The resultant solution was dried (Na_2SO_4) for 4 hr and the solvent removed by distillation. The products obtained were separated by column chromatography and TLC and characterized by IR and PMR spectral data. Identification of the compounds was done with GLC by coinjecting the authentic samples and the relative percentage of the products were determined.

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Reaction on thin layer chromatoplates: Formation of sulphides

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Activated halonitrobenzene are allowed to react, under controlled conditions with several selected aromatic and/or heterocyclic mercaptans on thin layer chromatoplates to give a series of sulphides. The identity of the products has been established by running the chromatograms along with authentic specimens.

Microchemical reactions, specially in the field of natural products[1-4] have been carried out on thin layer chromatoplates. Presently we report the synthesis of aromatic compounds containing sulphides on chromatoplates. Sulphides are important from medicinal chemistry point of view.

Experimental

The reaction was carried out by spotting the mercaptan in ethanol at the base line of thin layer chromatoplates prepared on plastic sheet precoated with a thin film (0.25 mm) of silica gel with fluorescent indicator. The spot was treated with alcoholic sodium hydroxide. The plate was then placed in a closed desiccator saturated with ethanol. The whole system was left (20-25 min) at room temperature. The reaction mixture spot was treated with halonitrobenzene, heated for 1-6 hr, the plate freed from solvent. A spot of the authentic sample was applied at the same base line prior to development and development was undertaken using the solvent system indicated in Table 1. Differentiation of the product from the starting material, if any remaining, was always possible if the appropriate conditions were used.

Table 1—Sulphides formation on thin layer chromatoplates

Compd No.	Starting Material (R_f)	Sulphide from (R_f)	Solvent system*
1	Thiophenol (0.84)	2,4-Dinitro-diphenylsulphide (0.25)	I
2	4-Aminothiophenol (0.42)	2,4-Dinitro-4′-aminodiphenyl (0.85)	I
3	Thiosalicylic acid (0.04)	2,4-Dinitro-2′-carboxydiphenyl (0.83)	II
4	2-Mercaptopyridine (0.27)	2-Pyridinyl-2,4-dinitrophenyl (0.49)	III
5	3-Hydroxy-2-mercaptopyridine (0.19)	2,4-Dinitrophenyl (0.88)	III
6	Thiocresol (0.15)	2,4-Dinitro-4′-methyldiphenyl (0.51)	IV
7	2-Mercaptobenzthiazole (0.28)	2-Benzthiazolyl-2,4-dinitrophenyl (0.14)	I
8	2-Mercaptobenzimidazole (0.23)	2-Benzimidazolyl-2,4-dinitrophenyl (0.39)	I
9	2-Mercaptobenzoxazole (0.25)	2-Benzoxazolyl-2,4-dinitrophenyl (0.35)	I
10	Thiophenol (0.61)	2-Nitro-4-chloro-diphenyl (0.18)	V
11	4-Aminothiophenol (0.15)	2-Nitro-4-chloro-4′-aminodiphenyl (0.29)	III
12	Thiosalicylic acid (0.11)	2-Nitro-4-chloro-2′-carboxydiphenyl (0.77)	VI

(Contd.)

Table 1 – Sulphides formation on thin layer chromatoplates – (Contd.)

Compd No.	Starting Material (R_f)	Sulphide from (R_f)	Solvent system*
13	3-Hydroxy-2-mercaptopyridine (0.26)	2-(3-Hydroxy)-pyridinyl-2-nitro-4-chlorophenyl (0.86)	IV
14	2-Mercaptopyridine (0.27)	2-Pyridinyl-2-nitro-4-chlorodiphenyl (0.41)	III
15	Thiocresol (0.19)	2-Nitro-4-chloro-4′-methyl-diphenyl —	I
16	2-Mercaptobenzoxazole (0.21)	2-Benzoxazolyl-2-nitro-4-chlorophenyl (0.39)	III
17	2-Mercaptobenzthiazole (0.21)	2-Benzthiazolyl-2-nitro-4-chlorophenyl (0.16)	III
18	2-Mercaptobenzimidazole (0.23)	2-Benzimidazolyl-2-nitro-4-chlorophenyl (0.36)	I
19	Thiophenol (0.61)	2-Nitro-4-bromodiphenyl (0.24)	V
20	2-Mercaptopyridine (0.30)	2-Pyridinyl-2-nitro-4-bromophenyl (0.43)	I
21	3-Hydroxy-2-mercaptopyridine (0.19)	2-[3-Hydroxy)-pyridinyl]-2-nitro-4-bromophenyl (0.81)	III
22	Thiocresol (0.15)	2-Nitro-4-bromo-4′-methyldiphenyl (0.48)	I
23	4-Aminothiophenol (0.15)	2-Nitro-4-bromo-4′-aminodiphenyl (0.31)	III

*Solvent system: Pet. ether-benzene-ethanol in the ratios (v/v) of: (I) 3:2:1; (II) 1:1:0; (III) 8:8:1; (IV) 10:0:1; (V) 10:0:0; (VI) 4:0:1.

Results showed that sulphides formation proceeded smoothly on the chromatoplates and the resulting compounds were obtained in good yields which were comparable to those obtained in conventional reaction apparatus. Structures of the prepared sulphides, were established on the basis of their IR spectra and also by direct comparison (m.m.p.) with authentic samples.

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Synthesis of some aromatic aldehydes and phenols as potential male antifertility agents†

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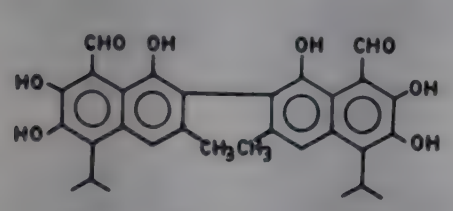
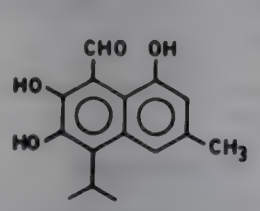
A series of appropriately substituted aromatic aldehydes and phenols have been prepared as potential antispermatogenic agents. Except for 2,3-dihydroxy-4-isopropylbenzaldehyde (**11**) which also happens to be toxic, the other compounds do not show promising activity.

The antispermatogenic activity of gossypol (**1**)[1] has stimulated worldwide interest in the development of a profile of structure-activity relationship for **1**, its sesquiterpene precursor hemigossypol (**2**)[2] and simple related compounds.



1



2

A look at the gossypol molecule (**1**) suggests that the activity may be due to (i) the formyl groups *ortho* and/or *peri* to the phenolic OH groups or (ii) the phenolic groups *ortho* to each other or (iii) the phenolic OH *ortho* to the isopropyl group or (iv) the restricted rotation around the binaphthyl bond. Keeping these factors in view, it was considered of interest to prepare some simple compounds incorporating these salient features and evaluate them for possible antispermatogenic activity.

2-Hydroxy-3-isopropyl-6-methyl-(**3**)- and 2-methyl-4-hydroxy-5-isopropyl-(**4**)-benzaldehydes, prepared by reacting dichloromethyl formate and thymol in the presence of anhydrous $AlCl_3$, on treatment with alkaline H_2O_2 yielded 3-methyl-6-isopropylcatechol (**5**) and 3-methyl-4-hydroxy-6-isopropylphenol (**6**), respectively. Further reaction of **5** with dichloromethyl formate and $AlCl_3$ gave 2-methyl-3,4-dihydroxy-5-isopropylbenzaldehyde (**7**). 2-Hydroxy-3-isopropyl-5-formyl-6-methylbenzaldehyde (**8**) was prepared both by Reimer-Tiemann method and by formylation of **3** with dichloromethyl formate in presence of $AlCl_3$. Likewise, Reimer-Tiemann reaction of 2-hydroxy-isopropylbenzene gave 2-hydroxy-3-isopropylbenzaldehyde (**9**) which on treatment with alkaline H_2O_2 yielded 3-isopropylcatechol (**10**). The latter on reaction with $POCl_3$ in DMF at room temperature furnished 2,3-dihydroxy-4-isopropylbenzaldehyde (**11**). 2-Hydroxy-5-isopropylbenzaldehyde (**12**) was prepared from 4-isopropylphenol. 4-Isopropylcatechol (**13**) was obtained by treating **12** with alkaline H_2O_2. Similarly 2-hydroxy-4-isopropylbenzaldehyde (**14**) was obtained from 3-isopropylphenol whereas reaction of 2-isopropylphenol with paraformaldehyde, HCl and hexamine yielded 3-isopropyl-4-hydroxybenzaldehyde (**15**). Isothymol on usual Reimer-Tiemann reaction furnished 2-hydroxy-3-methyl-6-isopropylbenzaldehyde (**16**) (Table 1), while 2,7-dihydroxynaphthalene gave 2,7-dihydroxy-1-naphthaldehyde (**17**) and 2,7-dihydroxynaphthalene-1,8-dialdehyde (**18**). Similarly 2,3-dihydroxynaphthalene yielded 2,3-dihydroxy-1-naphthaldehyde (**19**) and 2,3-dihydroxynaphthalene-1,4-dialdehyde (**20**).

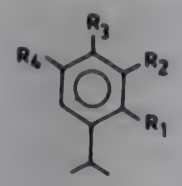
4-(3′,4′-Dimethoxyphenyl)-3-carbethoxy-but-3-en-oic acid (**21**), prepared in 80% yield from veratraldehyde, diethyl succinate and NaOMe, on refluxing with acetic anhydride and anhydrous sodium acetate gave ethyl 1-acetoxy-6,7-dimethoxy-3-naphthoate (**22**). Hydrolysis of the latter with ethanolic NaOH gave 1-hydroxy-6,7-dimethoxynaphthalene-3-carboxylic acid (**23**). Formylation of **23** with dichloromethyl formate/$AlCl_3$ in nitrobenzene yielded 2,3-dimethoxy-6-carboxy-8-hydroxynaphthalene-1-carboxaldehyde (**24**). 4-[3′-Methoxy-4′-hydroxyphenyl]-3-carbethoxy-but-3-enoic acid (**25**), prepared from vanillin following the method described for **21**, on treatment with Ac_2O and anhydrous NaOAc gave ethyl 4,6-diacetoxy-7-methoxy-2-naphthoate (**26**) which on hydrolysis with ethanolic NaOH furnished 4,6-dihydroxy-7-methoxynaphthalene-2-carboxylic acid (**27**) (Table 2). Except for compound **11**, which also proved toxic, other compounds did not show promising activity.

Experimental

All melting points were determined on an electrically heated block and are uncorrected. All the compounds were routinely checked for their structures by

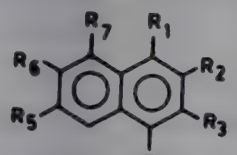
† CDRI Communication No. 4372.

Table 1—Physical data of compounds **3-16**



Compd	Mol formula	R_1	R_2	R_3	R_4	m.p./b.p. (°C)	Yield (%)	MS m/z (M^+)
3	$C_{11}H_{14}O_2$	OH	CHO	CH_3	H	130/15 mm	25	178
4	$C_{11}H_{14}O_2$	OH	H	CH_3	CHO	135	25	178
5	$C_{10}H_{14}O_2$	OH	OH	CH_3	H	Oil	60	166
6	$C_{10}H_{14}O_2$	OH	H	CH_3	OH	139	60	166
7	$C_{11}H_{14}O_3$	OH	OH	CH_3	CHO	102	40	194
8	$C_{12}H_{14}O_3$	OH	CHO	CH_3	CHO	80	15	206
9	$C_{10}H_{12}O_2$	OH	CHO	H	H	110	30	164
10	$C_9H_{12}O_2$	OH	OH	H	H	45	80	152
11	$C_{10}H_{12}O_3$	OH	OH	CHO	H		50	180
12	$C_{10}H_{12}O_2$	H	CHO	OH	H	117/760 mm	40	164
13	$C_9H_{12}O_2$	H	OH	OH	H	68	85	152
14	$C_{10}H_{12}O_2$	H	OH	CHO	H	108/2 mm	50	164
15	$C_{10}H_{12}O_2$	OH	H	H	CHO	98	40	164
16	$C_{11}H_{14}O_2$	CHO	OH	CH_3	H	130/15 mm	40	178

Table 2—Physical data of compounds **17-27**



Compd	Mol formula	R_1	R_2	R_3	R_4	R_5	R_6	R_7	m.p. (°C)	Yield (%)	MS m/z (M^+)
17	$C_{11}H_8O_3$	CHO	OH	H	H	H	OH	H	122	30	188
18	$C_{12}H_8O_4$	CHO	OH	H	H	H	OH	CHO	153	10	216
19	$C_{11}H_8O_3$	CHO	OH	OH	H	H	H	H	134	40	188
20	$C_{12}H_8O_4$	CHO	OH	OH	CHO	H	H	H	158	10	216
22	$C_{17}H_{18}O_6$	$OCOCH_3$	H	COOEt	H	OCH_3	OCH_3	H	192	80	318
23	$C_{13}H_{12}O_5$	OH	H	COOH	H	OCH_3	OCH_3	H	180	86	248
24	$C_{14}H_{12}O_6$	OH	H	COOH	H	OCH_3	OCH_3	CHO	175	50	276
26	$C_{18}H_{18}O_7$	$OCOCH_3$	H	COOEt	H	OCH_3	$OCOCH_3$	H	160	50	346
27	$C_{12}H_{10}O_5$	OH	H	COOH	H	OCH_3	OH	H	290	50	234

elemental analyses ($\pm 0.4\%$) and spectral (IR and PMR) data. IR spectra were recorded on a Perkin-Elmer 157 infracord and PMR spectra on R-32 or EM-360L spectrometer using TMS as internal standard while mass spectra were recorded on a Jeol-JMS-D300 instrument.

For the preparation of various substituted aromatic aldehydes either of the following general procedures was employed.

Method A

Anhydrous $AlCl_3$ (0.15 mole) was added to a well-stirred and ice-cooled solution of the phenol (0.1 mole) in dry CH_2Cl_2 (50-60 ml) followed by dropwise addition of dichloromethyl formate (0.12 mole) during 30 min and stirring continued for another 30 min at room temperature. The reaction mixture was then poured onto crushed ice containing conc. HCl (5 ml) and extracted with EtOAc. After removal of the solvent, the residue was purified by column chromatography over silica gel or distillation *in vacuo*.

Method B

In a typical Reimer-Tiemann reaction, the appropriate phenol (0.1 mole) suspended in water (20 ml) was added to a hot solution of NaOH (50%, 70 ml.)

under stirring followed by dropwise addition of $CHCl_3$ (25 ml) and the temperature kept below 60°C. After 1 hr, it was refluxed on a water-bath for 15 min, acidified with dil. HCl and extracted with $CHCl_3$. After removal of the solvent, the residue was purified by chromatography over silica gel or distillation *in vacuo*.

Method C

$POCl_3$ (15-20 ml) was added dropwise to a well-stirred solution of the phenol (0.1 mole) in DMF (30 ml) at room temperature. After stirring for 1 hr more, it was decomposed by adding saturated NaOAc solution and extracted with EtOAc. Removal of solvent and purification by chromatography or distillation *in vacuo* gave the desired pure product.

Method D

Alternatively, a mixture of the phenol (0.01 mole) and paraformaldehyde (500 mg) in conc. HCl (20 ml) was refluxed for 10 hr. The supernatant was decanted off and the residue washed with water. Hexamine (2 g) and $CHCl_3$ (5 ml) were added and the mixture refluxed for 4-5 hr. Solvent was distilled off and the residue was first refluxed with AcOH (50%, 20 ml). for 4 hr, followed by with conc. HCl (8 ml) for 2 hr. Water (20 ml) was added and the separated solid purified by chromatography.

For conversion of the aldehydes into the respective phenols, the former (0.01 mole) in aq. NaOH solution (1.6 g in 8 ml water) was treated with dropwise addition of H_2O_2 (30 ml., 6%) under stirring during 30 min, keeping the temperature below 45°, acidified with dil. HCl and the separated product purified by flash chromatography over silica gel.

4-(3′,4′-*Dimethoxyphenyl*)-3-*carbethoxy*-*but*-3-*enoic acid* (**21**)

Veratraldehyde (0.01 mole) was added dropwise to a stirred solution of diethyl succinate (0.03 mole) in absolute MeOH (200 ml) containing sodium (4 g). After keeping aside for 2 hr at room temperature, the reaction mixture was refluxed for 5 min, cooled, diluted with water (200 ml), acidified with dil.HCl (5%) and purified by acid-base treatment followed by EtOAc extraction; to yield (**21**), m.p. 160°C; yield 81%; MS: m/z 294.

Ethyl 1-*acetoxy*-6,7-*dimethoxy*-3-*naphthoate* (**22**)

21 (0.1 mole) was refluxed for 5 hr with NaOAc (5 g) and Ac_2O (30 ml). The mixture was diluted with water (500 ml) and left overnight. The separated brown solid was filtered, washed with water and crystallized from ethanol.

1-*Hydroxy*-6,7-*dimethoxy*-*naphthalene*-3-*carboxylic acid* (**23**)

22 (0.01 mole) was refluxed with ethanol (200 ml) and NaOH (3%, 300 ml) for 4 hr. Ethanol was distilled off and the remaining solution acidified with dil. HCl, filtered, dried and crystallized from ethanol, m.p. 180°.

4-(3′-*methoxy*-4′-*hydroxyphenyl*)-3-*carbethoxy*-*but*-3-*enoic acid* (**25**)

It was prepared in 30% yield from vanillin following the method described for **21**; m.p. 112°C; yield 25%; MS: m/z 280.

Ethyl 1,7-*diacetoxy*-6-*methoxy*-3-*naphthoate* (**26**)

It was prepared from **25** following the method described for **22**.

1,7-*Dihydroxy*-6-*methoxy*-*naphthalene*-3-*carboxylic acid* (**27**)

Alkaline hydrolysis of **26** as described for **23**, yielded this compound.

1,2-*Bis*-[5-*isopropyl*-4-*methoxy*-2-*methylbenzoyl*]*ethylene* (**28**)

To a well-stirred and ice cooled mixture of thymylmethyl ether (0.2 mole) and fumaryl chloride (0.11 mole), $AlCl_3$ (0.1 mole) was added in portions. The mixture was stirred for 1 hr at room temperature and left overnight. It was decomposed with ice containing dil. HCl and extracted with EtOAc. The organic layer was dried, concentrated and purified by chromatography over SiO_2 to give **28**; m.p. 110-11°C; yield 35%; MS: m/z 408.

1,2-*Bis*-[4-*hydroxy*-5-*isopropyl*-2-*methylbenzoyl*]*ethylene* (**29**)

A mixture of **28** (0.02 mole) and pyridine hydrochloride (0.1 mole) was heated at 190°C for four hours, cooled, diluted with water and filtered. The residue was purified by passing through a column of SiO_2 to give **29**; m.p. 90-91°C; yield 45%; MS: m/z 380.

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Synthesis and biological activity of 4-aryl-1-benzalhydrazinophthalazines and 3,6-diaryl-1,2,4-triazolo[3,4-*a*]phthalazines†

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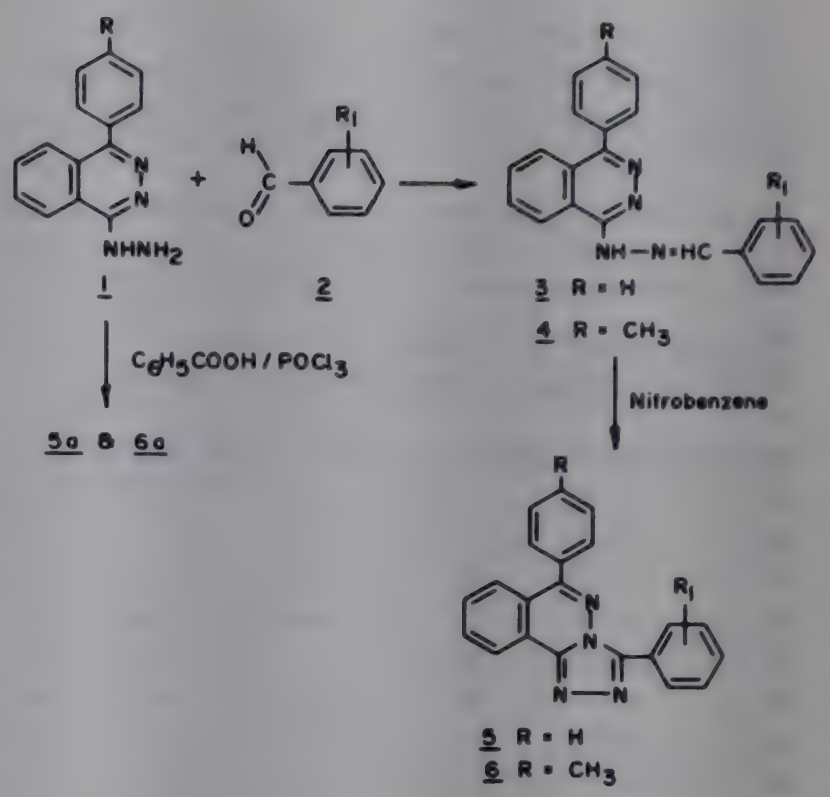
4-Aryl-1-hydrazino-phthalazines (**1**) undergo condensation with aromatic aldehydes (**2**) to give 4-aryl-1-benzalhydrazino-pthalazines (**3** and **4**) which on oxidative cyclization afford 3,6-diaryl-1,2,4-triazolo[3,4-*a*]phthalazines (**5** and **6**). These compounds have been screened for their antiinflammmatory, analgesic, motor and antihypertensive activities.

Litwin and coworkers[1] reported that 1-hydrazinophthalazine (hydralazine), an antihypertensive drug, is converted to its acetyl derivative in the body and further undergoes an enzymatic cyclization to 3-methyl-1,2,4-triazolo[3,4-*a*]phthalazine which is responsible for biological activity. 1,2,4-Triazole derivatives[2,3] are of current interest due to their wide ranging biological activities such as CNS depressant, antiinflammatory and pesticidal. In view of these findings and in continuation of our on-going work on the synthesis of biologically active azoles[4-7] and azines[8], we undertook the synthesis of the title compounds (**3-6**) as potential biodynamic agents although 1,2,4-triazolo[3,4-*a*]phthalazine ring system is known in literature[9].

The synthesis of 3,6-diaryl-1,2,4-triazolo[3,4-*a*]phthalazines (**5** and **6**) (Scheme 1) was accomplished in 70-90% yields by oxidative cyclization of **3** and **4** respectively employing nitrobenzene as oxidizing agent. In an alternate route **5a** and **6a** were obtained in a single step in 70-71% yield, by the reaction of 4-aryl-1-hydrazinophthalazines (**1**) with benzoic acid in the presence of $POCl_3$. Compounds **3** and **4** in turn were prepared in 75-85% yields by condensing **1** with aromatic aldehydes (**2**). The phthalazines (**1**) in turn were prepared from the corresponding 4-aryl-1-chlorophthalazines[9] following the literature method[10]. The structural assignments of all the compounds prepared are based on elemental analyses, IR and mass spectral data. All the compounds were checked for their purity by TLC on silica gel-G. The characterization data along with their biological activity for compounds **3-6** are given in Table 1.



a: R_1 = H ; b: R_1 = 4-OCH_3 ; c: R_1 = 3,4-$(OCH_3)_2$; d: R_1 = 4-CH_3 ; e: R_1 = 2-NO_2

Scheme 1

Compounds **3** and **4** showed bands at 3300 (NH), 1660 (N=CH) and 1580 cm^{-1} (aromatic stretching) while their cyclic derivatives **5** and **6** exhibited bands at 1640 (N=C) and 1580 cm^{-1} (aromatic stretching) in their IR spectra. Mass spectra of the compounds **5** and **6** were in conformity with their structures.

Biological activity

Antiinflammatory, analgesic, motor and antihypertensive activities of the compounds **3-6** were determined by literature methods[11-13]. Compounds **3a**, **3b**, **5a**, **5d** and **5e** exhibited promising antiinflammatory activity (44, 40, 51 and 52% respectively) in rats while phenylbutazone at the same dose (100 mg/kg, p.o.) produced 40% inhibition of 1% carrageenin-induced edema. The compounds showed very mild to moderate analgesic activity (4-40%) in comparison to aspirin (60%) at 100 mg/kg. Spontaneous motor activity in mice was studied using an actophotometer. The results revealed that **4e**, **5b**, **5c**, **5d** and **6e** cause 46-75% decrease in motor activity with mild sedation. An-

† RRL(H) Communication No. 2233.

Table 1—Characterization data and biological activity of compounds **3-6**

Compd	m.p. °C	Yield (%)	Mol. formula	Nitrogen (%)		% Decrease in motor activity at 100 mg/kg (i.p. mice)	Analgesic action at 100 mg/kg (% protection of pain)	Antiinflammatory activity at 100 mg/kg (% inhibition)	Decrease in blood pressure (mm Hg) at 5 mg/kg (i.v. dogs)
				Found	Calc				
3a	160-61	80	$C_{21}H_{16}N_4$	19.9	19.8	15	12	44	—
3b	142-44	82	$C_{22}H_{18}N_4O$	17.2	17.2	10	30	40	—
3c	182-83	76	$C_{23}H_{20}N_4O_2$	14.4	14.6	15	32	20	—
3d	132-33	85	$C_{22}H_{18}N_4$	16.7	16.6	6	15	37	—
3e	148-49	81	$C_{21}H_{15}N_5O_2$	18.8	19.0	15	10	39	—
4a	143-45	82	$C_{22}H_{18}N_4$	16.3	16.6	25	15	30	—
4b	162-63	75	$C_{23}H_{20}N_4O$	15.0	15.2	36	25	5	—
4c	175-76	81	$C_{24}H_{22}N_4O_2$	13.9	14.1	31	35	8	—
4d	160-62	80	$C_{23}H_{20}N_4$	15.7	15.9	26	12	17	—
4e	173-75	77	$C_{22}H_{17}N_5O_2$	18.4	18.2	46	7	37	—
5a	259-60	71	$C_{21}H_{14}N_4$	17.4	17.4	34	4	51	45
5b	270-72	90	$C_{22}H_{16}N_4O$	15.7	15.6	51	20	29	105
5c	220-22	77	$C_{23}H_{18}N_4O_2$	14.6	14.6	59	7	21	30
5d	250-52	70	$C_{22}H_{16}N_4$	16.6	16.7	75	40	51	10
5e	260	88	$C_{21}H_{13}N_5O_2$	19.2	19.1	37	20	52	25
6a	252	75	$C_{22}H_{16}N_4$	16.5	16.7	28	12	13	30
6b	300	82	$C_{23}H_{18}N_4O$	15.2	15.3	29	16	10	40
6c	287-88	89	$C_{24}H_{20}N_4O_2$	14.3	14.1	38	14	36	25
6d	255-56	80	$C_{23}H_{18}N_4$	15.8	16.0	42	15	27	10
6e	260-62	90	$C_{22}H_{15}N_5O_2$	18.3	18.4	48	8	17	24

tihypertensive activity of the compounds **5** and **6** was determined at a dose of 5 mg/kg i.v. and the results [as decrease in blood pressure (mm Hg)] are given in Table 1. In the primary screening, compounds **5a**, **5b**, **5c**, **6a** and **6b** produced a rapid fall in blood pressure (45, 105, 30, 30 and 40 mm Hg respectively) followed by quick recovery whereas hydralazine at 2 mg/kg i.v. produced a gradual and transient fall in blood pressure (42 mm Hg) with long duration and slow recovery.

Experimental

Melting points were taken in open capillaries on a Buchi 510 melting point apparatus and are uncorrected. IR spectra in KBr were recorded on a Perkin-Elmer 221 spectrophotometer, and mass spectra on a Hitachi RMU 6L mass spectrometer at 70 eV.

4-*Aryl*-1-*benzalhydrazinophthalazines* (**3a-e** *and* **4a-e**)

A mixture of **1** (0.05 mol) and an appropriate aromatic aldehyde (**2**; 0.055 mol) in ethanol (250 ml) was heated under reflux for 2 hr and cooled to room temperature. The product, thus separated, was filtered, washed with ether and recrystallized from ethanol to give **3** or **4** (Table 1) in 75-85% yields.

3,6-*Diphenyl*-1,2,4-*triazolo*[3,4-*a*]*phthalazine* (**5a**)

Method-1

A mixture of **3a** (3.9 g; 0.012 mol) and nitrobenzene (40 ml) was refluxed in an oil-bath for 4 hr. Nitrobenzene was removed by stream distillation, the crude product washed twice with pet. ether and recrystallized from acetic acid to give **5a**, m.p. 259-60°; MS: m/z 322 (M^+), 321 (M^+-H), 294 (M^+-N_2), 245 ($M^+-C_6H_5$), 219 ($M^+-C_7H_5N$), 193 ($M^+-C_8H_5N_2$), 165 ($M^+-C_8H_5N_4$), 142 ($M^+-C_{13}H_{10}N$) and 88 ($M^+-C_{14}H_{10}N_4$).

Compounds **5b-e** and **6a-e** (Table 1) were prepared and identified in a similar manner.

Method-2

A mixture of 1-hydrazino-4-phenylphthalazine (**1**; R = H, 0.01 mol), benzoic acid (0.011 mol) and $POCl_3$ (8 ml) was heated under reflux in an oil-bath for 4 hr. After cooling, it was poured into ice cold water to give a solid product which on washing with a dil. solution of $NaHCO_3$ followed by water and recrystallization from acetic acid gave

5a, yield 70%, m.p. 260-61°, identical in all respects with that obtained by method-1.

Compound **6a** was prepared similarly in 71% yield and was found to be identical in all respects with **6a** prepared by cyclization of **4a** with nitrobenzene (method-1).

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Synthesis of [1,2,4]triazino[4,3-*a*]benzimidazol-4(10*H*)-ones as antimicrobial agents

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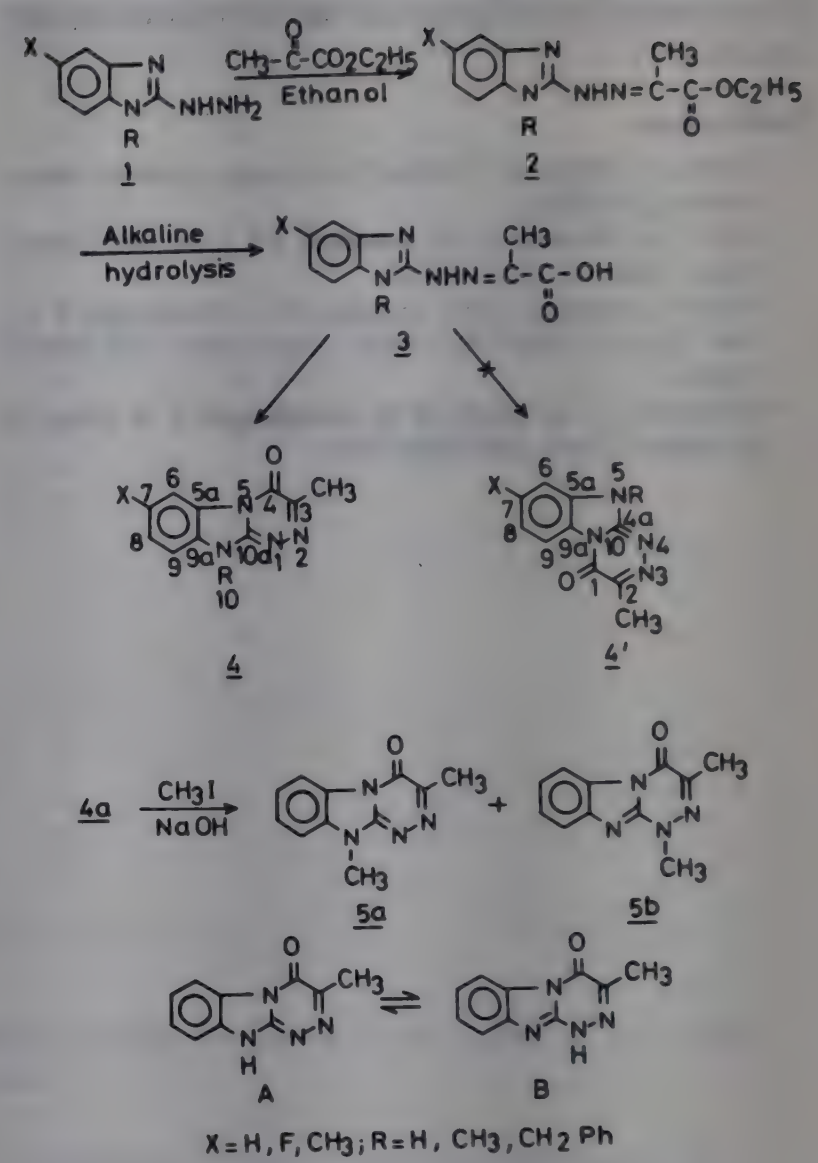
[1,2,4]Triazino[4,3-*a*]benzimidazol-4(10*H*)-ones(**4**) have been obtained by the reaction of 2-hydrazinobenzimidazole with ethyl pyruvate in neutral medium followed by hydrolysis and cyclization. Further, it has been found that these compounds exist in two tautomeric forms due to the labile hydrogen. The compounds display promising activity when screened for their antibacterial and antifungal activities.

Various 2-substituted benzimidazoles possessing antimicrobial activity have been reported by several group of workers[1,2]. 2-Hydrazinobenzimidazoles are highly reactive compounds[3]; some of the derivatives have been used as azodyes[4] while some other derivatives show tuberculostatic[5] and influenza virus inhibition activities[6]. In pursuit of our search for new and better antimicrobial agents, we have now synthesized[1,2,4]triazinobenzimidazol-4(10*H*)-ones(**4**) by the reaction of 2-hydrazinobenzimidazoles with ethyl pyruvate. This procedure which involved three steps (Scheme 1) gave **4** in better yields than that reported by other workers from the reaction of ethyl pyruvate with other hydrazines[7].



Scheme 1

2-Hydrazinobenzimidazoles on refluxing with ethyl pyruvate in ethanol for 6-7 hr gave ethyl α-oxopropionate benzimidazol-2-ylhydrazones(**2**). Alkaline hydrolysis of **2** in 50% ethanol gave α-oxopropionic acid benzimidazol-2-ylhydrazones(**3**) which underwent cyclization with gl. acetic acid affording **4** (Scheme 1).

In the PMR spectrum of **4d**, the aromatic protons appeared as a multiplet in the region δ 7.1-7.3, as in the case of hydrazone **3d**. This indicates the cyclization to be linear giving **4** and not the angular isomer (**4'**). If **4'** had been formed, C_9-H would have appeared slightly downfield due to deshielding effect of the carbonyl group.

The characterization data of all the new compounds are given in Table 1. The IR, PMR, ^{13}C NMR and mass spectral data of only representative compounds have been given (see Experimental).

Methylation of 3-methyl-[1,2,4]triazino[4,3-*a*]benzimidazol-4(10*H*)-one (**4a**) in alkaline medium with methyl iodide, gave two compounds (**5a**, **5b**). One of them was found to be 3,10-dimethyl-[1,2,4]triazino[4,3-*a*]benzimidazol-4(10*H*)-one (**5a**) and the other as 1,3-dimethyl-[1,2,4]triazino[4,3-*a*]benzimidazol-4(10*H*)-one(**5b**) on the basis of PMR data. The N-methyl protons in **5b** appeared at δ 3.5 as compared to **5a** where these appeared at 4.0, the data being in agreement with the respective environment[8]. The formation of these products prompted us to make a new and important conclusion that [1,2,4]triazino[4,3-*a*]benzimidazol-4(10*H*)-ones exist in two tautomeric forms **A** and **B**. The former being the predominent form as indicated by the high yield of **5a**.

Antimicrobial activity

Compounds **4a** and **4c-4e** of the series were evaluated for their antimicrobial activity following the method of Gould *et al.*[9] using streptomycin in antibacterial and mycostatin in antifungal activity as reference compounds.

Table 1—Characterization data of the various compounds prepared

Compound	X	R	m.p. °C	Yield (%)	Mol. formula (M^+)	N (%)*	
						Found	Calc.
2a	H	H	> 360	80	$C_{12}H_{14}N_4O_2$ (246)	22.7	22.8
2b	H	CH_3	134	81	$C_{13}H_{16}N_4O_2$ (260)	21.5	21.5
2c	H	CH_2Ph	> 360	79	$C_{19}H_{20}N_4O_2$	16.7	16.7
2d	CH_3	H	160	78	$C_{13}H_{16}N_4O_2$	21.6	21.5
2e	F	H	215	78	$C_{12}H_{13}FN_4O_2$ (264)	21.1	21.2
3a	H	H	> 360	82	$C_{10}H_{10}N_4O_2$ (218)	20.7	20.7
3b	H	CH_3	210	88	$C_{11}H_{12}N_4O_2$ (232)	24.1	24.1
3c	H	CH_2Ph	125	81	$C_{17}H_{16}N_4O_2$	18.2	18.2
3d	CH_3	H	188	78	$C_{11}H_{12}N_4O_2$ (232)	24.1	24.1
3e	F	H	> 360	75	$C_{10}H_9FN_4O_2$	23.7	23.7
4a	H	H	> 360	80	$C_{10}H_8N_4O$ (200)	28.2	28.0
4b	H	CH_3	245	83	$C_{11}H_{10}N_4O$ (214)	26.2	26.2
4c	H	CH_2Ph	168	82	$C_{18}H_{16}N_4O$ (290)	19.3	19.3
4d	CH_3	H	258	84	$C_{11}H_{10}N_4O$ (214)	26.0	26.2
4e	F	H	> 360	81	$C_{10}H_7FN_4O$ (218)	25.7	25.7

*Satisfactory C,H analyses were obtained for all the compounds.

All compounds were active against gram positive bacteria *Staphylococcus aureus* while none was active against gram negative bacteria. Compound **4e** showed maximum zone of inhibition (15.0 mm) against *Staphylococcus aureus*. Its enhanced activity may be attributed to the presence of fluorine. Compounds **4d** and **4e** were active against all the fungi tested. All the compounds showed maximum activity against *Aspergillus flavus*. Compound **4a** showed maximum zone of inhibition (10.0 mm) against the fungus *Drechslera tetramera*. The results are recorded in Table 2.

Experimental

IR spectra in KBr (ν_{max} in cm^{-1}) were recorded on a Perkin-Elmer 577 spectrophotometer, PMR spectra in TFA on a Jeol FX 90Q spectrometer (89.55 MHz) using TMS as internal reference and ^{13}C NMR spectra in DMSO-d_6 at 22.49 MHz (chemical shifts in both cases in δ, ppm). The mass spectra were recorded on MS-30 and MS-50 Kratos mass spectrometers at an ionisation potential of 70 eV. Melting points were determined in open glass capillaries on a Gallenkamp melting point apparatus and are uncorrected. Elemental analyses were performed at CDRI, Lucknow.

The general methods followed for the synthesis of typical compounds are described below.

Ethyl α-oxopropionate benzimidazol-2-ylhydrazone (**2a**)

A solution of 2-hydrazinobenzimidazole[10] (1.48 g, 0.01 mole) and ethyl pyruvate[11] (1.16 g, 0.01 mole) in ethanol (50 ml) was refluxed for 6-7 hr, cooled, filtered and washed with ethanol. The product, thus obtained, was recrystallised from ethanol, yield 1.96 g (80%), m.p. > 360°; IR: 3150 (NH), 1720 (ester CO); PMR: 0.9-1.3 (t, 3H, CH_3), 2.0(s, 3H, $=C(CH_3)-$), 4.2-3.6(q,2H,CH_2), 7.0-7.7 (m,4H,ArH), 9.5(s,1H,NH), 10.0(s,1H, $-NHN=$); MS:m/z 246(M^+) (Found: C, 58.8; H, 5.7; N, 22.7. $C_{12}H_{14}N_4O_2$ requires C, 58.8; H, 5.7; N, 22.8%).

Table 2—Antimicrobial activity of[1,2,4]triazino [4,3-*a*]benzimidazol-4(10*H*)-ones

	Inhibition zone (in mm) of			
	4a	**4c**	**4d**	**4e**
Test Organism	Gram negative bacteria			
Escherichia coli	–	–	–	–
Enterobacter cloacae	10.0 (5.0)	–	8.0 (4.0	–
	Gram positive bacteria			
Staphylococcus aureus	9.0 (7.5)	6.0 (5.0)	6.0 (5.0)	15.0 (12.5)
Streptococcus faecalis	–	–	–	–
	Fungi			
Aspergillus flavus	7.0 (3.8)	7.0 (3.8)	8.0 (4.4)	10.0 (5.5)
Curvularis lunata	–	–	7.0 (3.5)	10.5 (5.0)
Drechslera tetramera	10.0 (5.0)	–	8.0 (4.0)	9.0 (4.5)
Candida albicans	8.0 (6.1)	–	7.0 (5.3)	8.0 (6.1)

Values in parentheses represent activity index which is defined as: $\frac{\text{Inhibition area of the sample}}{\text{Inhibition area of the standard}}$

(–) = Not measurable activity.

Compounds **2b-e** listed in Table 1 were similarly prepared.

α-Oxopropionic acid benzimidazol-2-ylhydrazone (**3a**)

A solution of **2a** (2.46g, 0.01 mole) and sodium hydroxide (0.4g, 0.02 mole) in 100 ml of 50% ethanol was refluxed for 5hr, then cooled and acidified with dil.HCl. The precipitate, thus obtained, was filtered and crystallised from ethanol to give **3a**, yield 1.78g (82%), m.p. > 360°; IR : 3300(NH), 3100(OH), 1700(CO); PMR 2.2(s,3H,CH_3), 7.5-7.8(m,4H,ArH), 9.4(s,1H,NH), 10.0(s,1H, –NHN=); MS: m/z 218-(M^+) (Found : C,56.8; H,4.6; N,20.7. $C_{10}H_{10}N_4O_2$ requires C,56.9; H,4.6; N,20.7%).

Compounds **3b-e** listed in Table 1 were prepared similarly.

3-*Methyl*-[1,2,4]*triazino* [4,3-*a*]benzimidazol-4(10*H*)-*one* (**4a**)

A solution of **3a** (2.18g, 0.01 mole) in gl. acetic acid (100 ml) was refluxed for 48-50 hr to give **4a** which was crystallised from acetic acid, yield 1.6g (80%), m.p. > 360°; IR: 3130(NH), 1690(CO); PMR : 2.5(s,3H,CH_3), 7.5-7.8(m,4H,ArH); ^{13}C NMR : 174 (C-4); 151 (C-10a), 146 (C-3), 140, 137, 125, 121, 116 and 113 (aromatic carbons) and 15 (CH_3); MS: m/z 200(M^+) and 201 (M+1) (Found C,60.1; H,4.2; N,28.2.$C_{10}H_8N_4O$ requires C,60.0; H,4.0; N,28.0%).

Compounds **4b-e** listed in Table 1 were similarly prepared.

Methylation of **4a**

A mixture of **4a** (2.0 g, 0.01 mole), methyl iodide (1.42 g, 0.01 mol), 10 ml 30% NaOH and ethanol (30 ml) was stirred overnight. The ethanol was distilled off, and the residue poured into ice cold water, filtered and recrystallised from ethanol. The product showed two spots on TLC (ethylacetate - methanol; 9:1), one yellowish green and the other brownish green. The two spots had a large R_f difference and were separated by PLC and each crystallised from ethanol.

Compound **5a** : 3,10-Dimethyl-[1,2,4]triazino[4,3-*a*]benzimidazol-4-one—Yellowish green, yield 1.75 (82%) m.p. 245°; PMR : 2.0 (s,3H,CH_3), 4.0(s,3H,NCH_3), 6.0-7.5(m,4H,ArH); MS : m/z 214(M^+) (Found C,61.7; H,4.7; N,26.1. $C_{11}H_{10}N_4O$ requires C,61.7; H,4.7; N,26.2%).

Compound **5b** : 1,3-Dimethyl-[1,2,4]triazino[4,3-*a*]benzimidazol-4-one — Brownish green, yield 0.38 g (18%), m.p. 180° (d): PMR : 2.1 (s,3H,CH_3), 3.5(s,3H,NCH_3), 6.5-7.5(m,4H,ArH); MS: m/z 214 (M^+) (Found C,61.7; H,4.7; N,26.2. $C_{11}H_{10}N_4O$ requires C,61.7; H,4.7; N,26.2%).

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Synthesis and anthelmintic activity of methyl 5-(α-hydroxy-α-substituted-methyl)-1*H*-benzimidazole-2-carbamates†

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Methyl 5-(α-hydroxy-α-substitutedmethyl)-1*H*-benzimidazole-2-carbamates (**6-10**)have been synthesized. Among these 5-(α-hydroxyarylmethyl)-1*H*-benzimidazole-2-carbamates (**6-8**) have been found to possess promising anthelmintic activity against *A. ceylanicum* (hookworm), *N. brasiliensis* (trichostrongylid), *S. obvelata* (oxyurid), *H. diminuta* and *H. nana* (cestodes), while 5-(α-hydroxyalkyl)-1*H*-benzimidazole-2-carbamates (**9** and **10**) are effective only against *A. ceylanicum*.

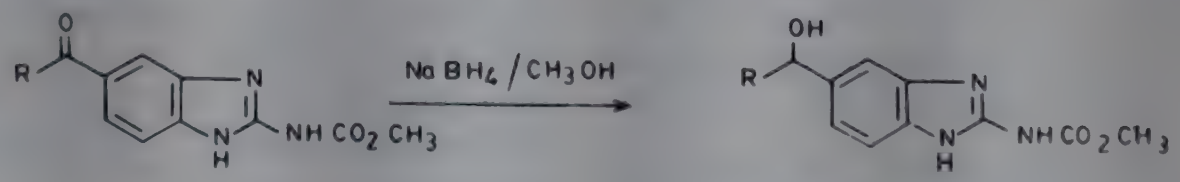
The broad spectrum anthelmintic activity of methyl 5-(α-hydroxyphenylmethyl)-1*H*-benzimidazole-2-carbamate (**6**), a major metabolite[2,3] of mebendazole (**1**), stimulated us to undertake the synthesis of methyl 5-(α-hydroxy-α-substitutedmethyl)-1*H*-benzimidazole-2-carbamates (**7-10**) and evaluate their anthelmintic activity.

Methyl 5-acylbenzimidazole-2-carbamates (**2-5**), needed for the present study, were synthesized by the methods reported in literature[4,5]. Difficulty, however, was encountered in the reduction of the carbamates **1-5** due to their poor solubility in most of the organic solvents. Reduction of **1** and **2** has been carried out earlier with sodium borohydride in pyridine[6] or in a mixture of isopropanol and water[7]. We found that the carbamates **1-5** could be reduced in fairly good yield to the corresponding hydroxy derivatives (**6-10**; Scheme 1) (Table 1) with sodium borohydride in refluxing methanol.

Table 1—Physical data of methyl 5-(α-hydroxy-α-substituted-methyl)-1*H*-benzimidazole-2-carbamates (**6-10**)

Compd	m.p. °C	Yield (%)	Mol. formula* (mol. wt)
6	> 300	87	$C_{16}H_{15}N_3O_3$ (297.30)
7	> 300	63	$C_{14}H_{13}N_3O_3S$ (303.33)
8	> 300	71	$C_{16}H_{16}N_4O_3$ (312.32)
9	> 300	69	$C_{11}H_{13}N_3O_3$ (235.23)
10	210	60	$C_{12}H_{15}N_3O_3$ (249.26)

*All the compounds gave satisfactory elemental analyses.



1, R = C_6H_5 (Mebendazole)
2, R = (Nocodazole)
3, R = $C_6H_4-NH_2$ (m)
4, R = CH_3
5, R = C_2H_5

6, R = C_6H_5
7, R =
8, R = $C_6H_4-NH_2$ (m)
9, R = CH_3
10, R = C_2H_5

Scheme – 1

†CDRI Communication No. 4283.

Anthelmintic activity

The carbamates **6-10** and their carbonyl precursors (**1-5**) were evaluated for their anthelmintic activity against *A. ceylanicum* (hamsters)[8], *N. brasiliensis* (rats)[8], *S. obvelata* (mice)[9,10], *H. diminuta* (rats)[11] and *H. nana* (mice)[11] at various dose levels. Three to five animals were used for each dose level. The efficacy was expressed in terms of per cent worm reduction in the host in the case of *A. ceylanicum* and *N. brasiliensis*. However, the criterian of the efficacy was absolute clearance of the parasites from the treated hosts in the case of *S. obvelata*, *H. diminuta* and *H. nana* because of wide variation in parasite load in these infections.

The results of anthelmintic activity of the compounds **1-10** are given in Table 2. The carbamates **6-8**, in general, exhibited broad spectrum anthelmintic activity. The hydroxy compound **7** was found to be almost equipotent compared to its carbonyl precursor (**2**) against *A. ceylanicum* infection and cleared all the worms at a dose level of 3.12 mg/kg while compounds **6** and **8** were less potent than their carbonyl precursors **1** and **3**. In the case of *N. brasiliensis* and *S. obvelata* infections, the hydroxy compounds **6** and **7** exhibited better activity than the carbonyl precursors, and showed 97-100% activity at the dose levels of 150 mg/kg × 1 to 50 mg/kg × 3 and 50 mg/kg × 1 to 25 mg/kg × 3, respectively. Mebendazole (**1**) and nocodazole (**2**) were found to be inactive against *H. nana* inflection at 400 mg/kg × 3 and 250 mg/kg × 3 dose levels, respectively while the hydroxy derivatives **6** and **7** were active at 100-250 mg/kg × 3 dose levels. No significant change in the activity was observed in the case of methyl 5-(α-hydroxyalkyl)-1*H*-benzimidazole-2-carbamates (**9** and **10**) and their carbonyl precursors (**4** and **5**, respectively).

It may be concluded from this study that methyl 5-(α-hydroxyarylmethyl)-1*H*-benzimidazole-2-carbamates exhibited a higher order of activity and broader anthelmintic activity than the corresponding carbonyl precursors while methyl 5-(α-hydroxyalkyl)-1*H*-benzimidazole-2-carbamates exhibited similar spectrum of anthelmintic activity as compared to the corresponding carbonyl precursors. It appears that the presence of an aryl group at 5α-position of 1*H*-benzimidazole-2-carbamates play an important role in their anthelmintic activity.

Experimental

Methyl 5-(α-hydroxy-α-substitutedmethyl)-1H-benzimidazole-2-carbamates (**6-10**; *Table* 1): *General procedure*

Powdered sodium borohydride (10 g) was added in small portions during 4 to 6 hr, to a refluxing suspension of methyl 5-acyl-1*H*-benzimidazole-2-carbamates (5 g) in methanol (50 ml). The solvent was removed under reduced pressure, and the residue triturated with ice-cooled water to give the product which was filtered, washed with water followed by ethanol and dried. Compounds **9** and **10** were isolated by chromatography on a SiO_2 column using chloroform-methanol (95 : 5) as eluant and crystallised from chloroform-methanol (95 : 5).

Compound **6**—IR(KBr): 3550, 3320, 1715, 1640, 1605, 1450, 1280, 1100, 800, 750 cm^{-1}; ^1H NMR (TFA): δ 3.86 (s, 3H, OCH_3), 6.97 (s, 1H, 5α-CH), 7.18 (s, 5H, 5α-ArH) and 7.37-7.60 (m, 3H, 4-, 6- and 7-ArH).

Compound **9**—IR(KBr): 3350, 1720, 1640, 1610, 1455, 1285, 1110 cm^{-1}; ^1H NMR (TFA): δ 1.53 (d, 3H, C-CH_3), 3.82 (s, 3H, OCH_3), 5.98 (q, 1H, 5α-CH) and 7.27-7.64 (m, 3H, ArH); MS: m/z 235 (M^+), 220 $(M-15)^+$, 160.

Table 2—Efficacy of compounds **1-10** against intestinal helminth parasites

Compd	C-5 Substituent	*A. ceylanicum* dose mg/kg (% activity)	*N. brasiliensis* dose mg/kg (% activity)	*S. obvelata* dose mg/kg (% activity)	*H. diminuta* dose mg/kg (% activity)	*H. nana* dose mg/kg (% activity)
6	$CH(OH)C_6H_5$	5 × 1 (99.1)	150 × 1 (100)	50 × 1 (100)	100 × 3 (100)	100 × 3 (100)
1	COC_6H_5	1 × 1 (100)	250 × 1 (100)	100 × 1 (66.6)	200 × 3 (100)	400 × 3 (00)
7	CH(OH)-2-thienyl	3.12 (100)	50 × 3 (97.1)	25 × 3 (100)	250 × 3 (100)	250 × 3 (100)
2	CO-2-thienyl	3.12 (100)	50 × 3 (56.9)	25 × 3 (66.6)	250 × 3 (100)	250 × 3 (00)
8	$CH(OH)C_6H_4NH_2(m)$	50 × 1 (100)	100 × 3 (47.5)	25 × 3 (81.8)	250 × 3 (100)	250 × 3 (00)
3	$COC_6H_4NH_2(m)$	25 × 1 (100)	100 × 3 (40.1)	25 × 3 (66.7)	250 × 3 (100)	250 × 3 (00)
9	$CH(OH)CH_3$	50 × 1 (100)	250 × 3 (00)	100 × 1 (00)	250 × 1 (00)	250 × 3 (00)
4	$COCH_3$	50 × 1 (72.1)	250 × 3 (00)	100 × 1 (00)	250 × 1 (00)	250 × 3 (00)
10	$CH(OH)C_2H_5$	50 × 1 (93.0)	250 × 3 (00)	100 × 1 (00)	250 × 1 (00)	250 × 3 (00)
5	COC_2H_5	50 × 1 (80.8)	250 × 3 (00)	100 × 1 (00)	250 × 1 (00)	250 × 3 (00)

Acknowledgement

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Corrigendum

Paper entitled, "Regioselective reactions of *o*-aminothiophenol with unsymmetrical maleic anhydrides", *Indian J Chem*, 28B (1989) 123-125.

In Scheme 1 on p. 123, the entry *b* should be $R^1 = H$; $R^2 = Me$ (MMA) and not as printed.

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